Andrea Tinelli
Luis Alonso Pacheco
Sergio Haimovich
Editors

Atlas of Hysteroscopy

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ISBN 978-3-030-29465-6 ISBN 978-3-030-29466-3 (eBook)
https://doi.org/10.1007/978-3-030-29466-3

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Part I

Vaginoscopy

1

Osama Shawki and Yehia Shawki

The history of vaginal examination dates back to ancient times and has, hitherto, been a rite of passage into womanhood. Revolutions in this gateway field have been few and far between, with the most notable of which coming from J. Marion Sims in 1845 when he fashioned the first crude speculum from a pewter spoon [1]. Cusco's duck bill vaginal speculum was introduced around 1859 which proved to be more refined and practical than most [2] and remains to this day a staple in most gynaecological offices and clinics, being a routine portion of an obgyn's examination. This aged format has not seen developments in the last century and can even go so far as to be labelled a misnomer, as the blades of the speculum hide most of the vagina, and thus is more useful in viewing the cervix. On the opposite end of the spectrum, the patients are subjected to an unpleasant and painful procedure which leaves stinging memories from one visit to the gynaecologist to the next. With the dawn of optics and endoscopy came exceptional developments in the medical field, most important of which for the gynaecologist are laparoscopy and hysteroscopy. Hysteroscopy is available as an office procedure with minimal to no sedation needed and provides exemplary diagnostic capabilities as well as the potential for operative intervention. In 1997, a new means of performing the procedure was introduced which was intended to decrease pain by avoiding the need for tenaculum and speculum [3]. This method, however, still did not allow full examination of the vagina due to the inability to maintain distension of the potential space (vagina). The proposal of a new modification to inspect the vagina was proposed by Osama Shawki dubbed the Shawki technique which includes approximation of the vulva to avoid leakage and ballooning of the vagina exposing all the vaginal walls, fornices as well as the portio vaginalis of the cervix. This technique bears all the advantages of the aforementioned technique in terms of pain relief and gains a more effective view of the vaginal canal and ectocervix. It has also been revolutionary for the treatment of vaginal pathology such as OHVIRA syndrome for the obstructed hemi-vagina to be re-connected to the menstruating vagina.

These patients tend to present around the age of puberty when the menstrual cycle begins. Patients complain of severe cyclic lower abdominal pain during menstruation often requiring hospitalisation. As one hemi-vagina is communicating with the vulval orifice, there is no suspicion of Mullerian anomalies until further investigations are performed which include ultrasound examination and MRI.

These advanced studies would show a fluid collection in the vagina. The condition is most commonly associated with a bicornuate bicollis uterus, otherwise known as didelphys.

Another common association is ipsilateral renal agenesis on the same side as the obstructed hemi-vagina; thus a urological examination would prove prudent.

These cases were previously misdiagnosed and subjected to exploratory laparotomies which may have ended in a hemi-hysterectomy, removing the obstructed side's uterus. The fact that a lot of the patients are virgins proved a difficult point to navigate any vaginal approach in certain cultures where the hymen is of great importance.

With the new vaginoscopy technique implemented, exposure of the vagina is possible and the obstructed vagina can be accessed by utilising a resectoscope with a Collin's knife inserted trans-hymenal and incising through the obstructing vaginal septum. This unification is a minimally invasive approach which respects the hymen and avoids the abdominal route whilst providing an instant cure for the condition.

Similarly, a longitudinal non-obstructing vaginal septum can be tackled by the vaginoscopic route as well.

This pathology, which is usually associated with a cervico-uterine septum, was previously treated surgically by clamping and excising the vaginal septum. This was then followed by hysteroscopic release of the uterine septum with or without incision of the cervical septum [4].

In the vaginoscopic approach, the vaginal septum is tackled in a similar way to a uterine septum, again utilising the resectoscope with Collin's knife inserted and incising the

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_1

septum from caudal to cephalad until reaching the external cervical os.

In this technique the tissues retract and there is no need for any further excision. Progression to resecting the cervical and uterine septa is then possible hysteroscopically.

Vaginoscopy has also proved to be advantageous in cases where vaginal examination of virgins is required. In cases of endometrial polyps, submucous fibroids and such. Here, the vaginoscopic approach saves any damage to the hymen, in cultures where integrity of the hymen is considered important. The diameter of the hysteroscope ranges from 3.4 to 9 mm depending on the modality of the sheath used and the different brands available, all of which can be inserted through the hymen without causing any damage.

Furthermore, cases of vaginal endometriosis can now be easily diagnosed vaginoscopically, through proper visualisation and examination of the vagina. Bluish or brownish endometriotic spots which would have been missed by a conventional vaginal examination can now be seen. This pathology can be implicated in cases of dyspareunia and can now be easily diagnosed and therefore treated by cauterising the endometrial tissue.

In conclusion, vaginoscopy is a new vision for an age-old practice, shifting gynaecological vaginal examination to the modern era (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, 1.12 and 1.13).

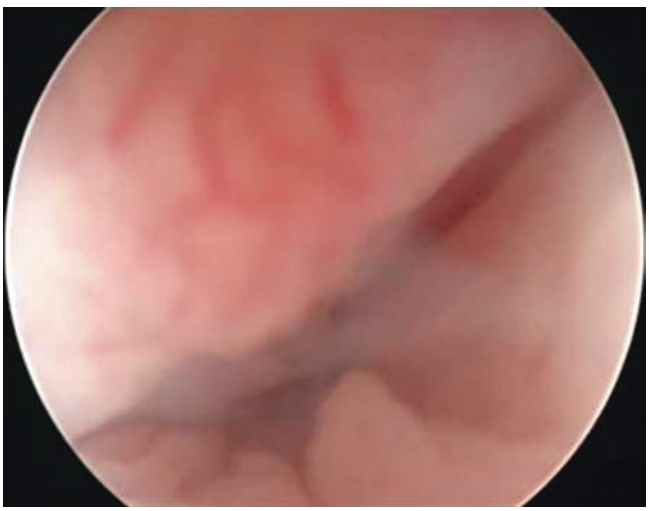

Fig. 1.1 Standard vaginoscopy without approximation of the vulva yielding a collapsed view of the vagina has limited capacity to inspect the vagina and is mainly used as a means of accessing the cervix

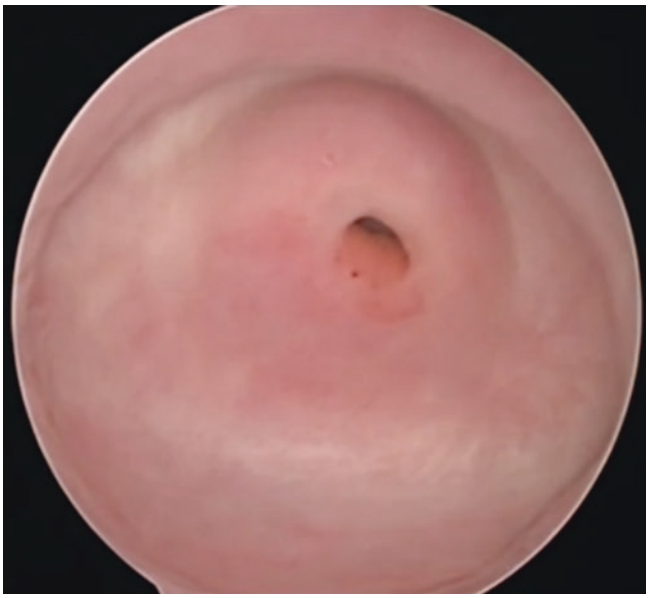

Fig. 1.2 Shawki technique to visualise the vagina, exposing the vaginal walls, fornices and portio vaginalis of the cervix

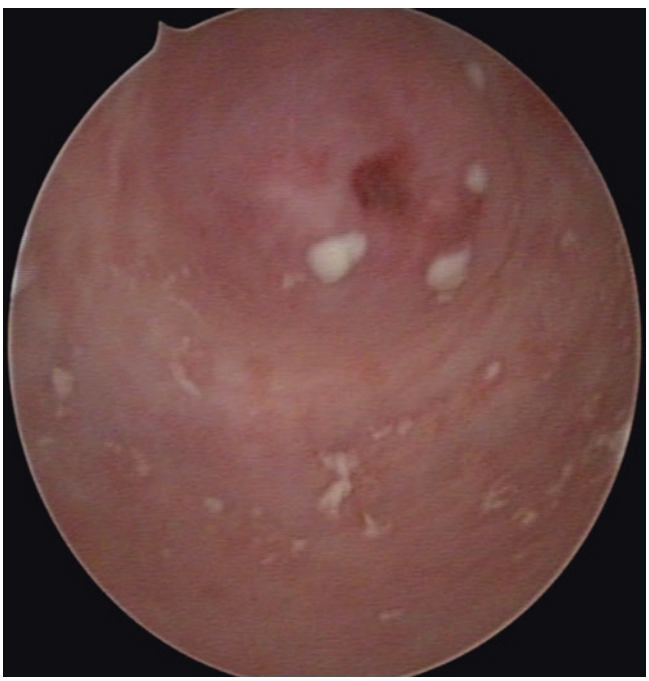

Fig. 1.3 A case of vaginal candidiasis depicting an example of infections of the vagina as seen by modern vaginoscopy. Creamy white congregations resulting from the yeast infection can be seen on the vaginal walls and on the cervix

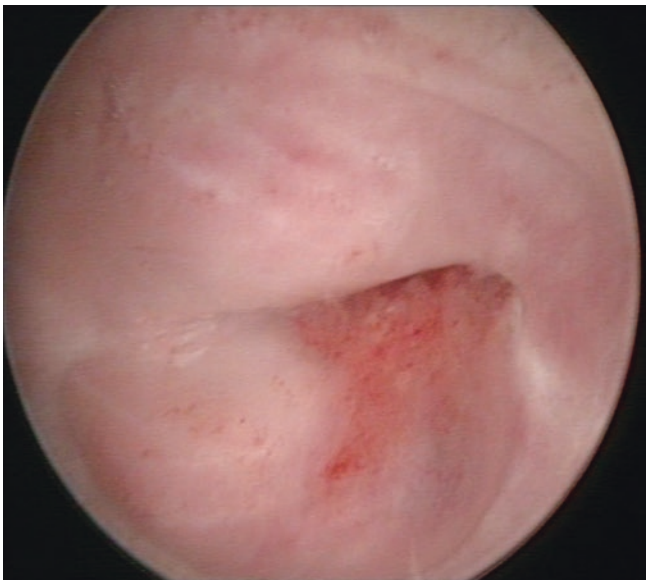

Fig. 1.4 Picture of bilateral cervical tears most likely as an obstetric complication. The anterior lip of the cervix is seen almost flush with the vaginal wall in compilation with the cervical tears

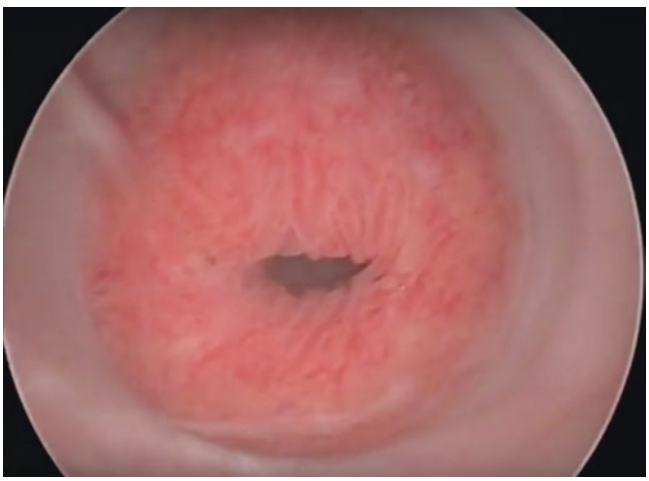

Fig. 1.5 Picture of cervical ectopy. Complete cervical erosion where the transformation zone has shifted from the external os to cover the portio vaginalis of the cervix by columnar epithelium

Fig. 1.6 Cervical erosions complicated by cervical polyps. The cervical polyps are seen lined by cervical epithelium and protruding from the external os

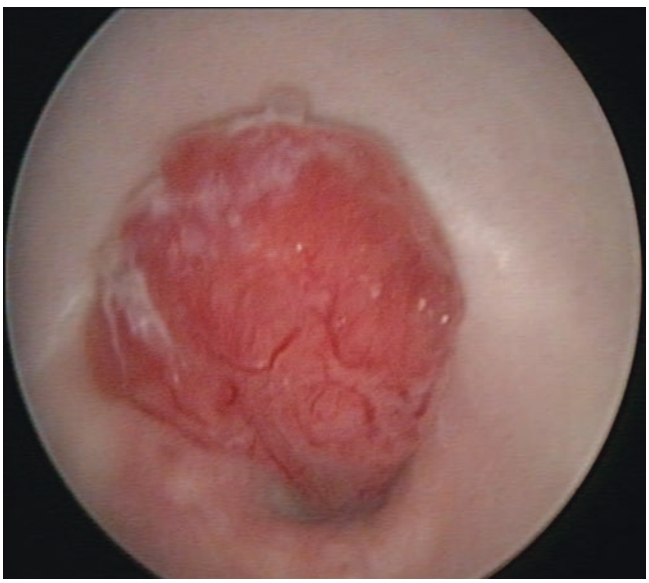

Fig. 1.7 Cervical fibroid prolapsed from the external os and into the vagina

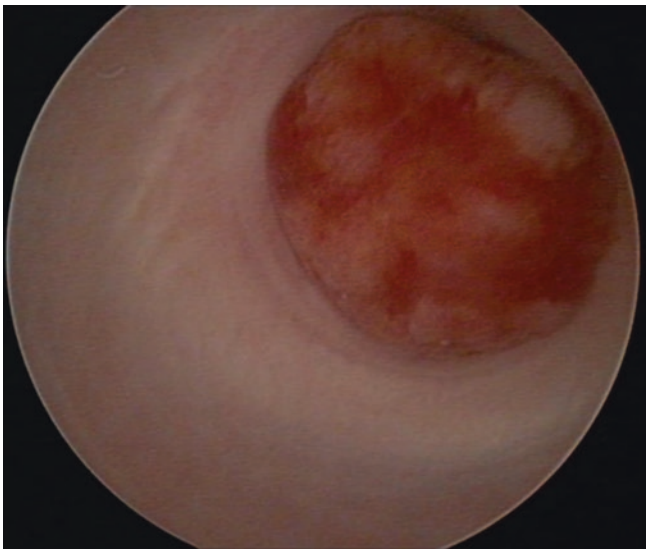

Fig. 1.8 Submucous fibroid prolapsed through the cervical canal and into the vagina. Characteristic appearance of endometrium on the fibroid indicates that the origin is from the uterine cavity

Fig. 1.10 Multiple spots of vaginal endometriosis seen in the anterior and lateral fornices. This pathology has been implicated in cases of dyspareunia and deep pelvic pain

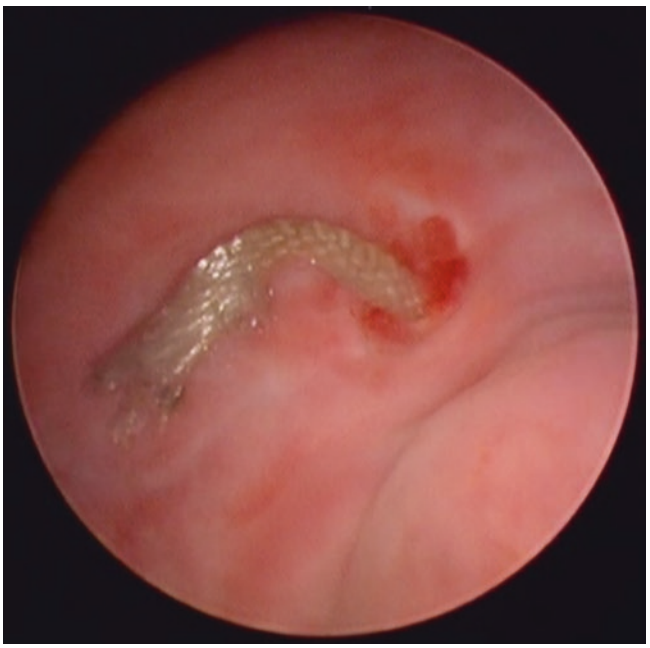

Fig. 1.9 Cerclage tape left near the anterior fornix following improper removal of vaginal cerclage tape

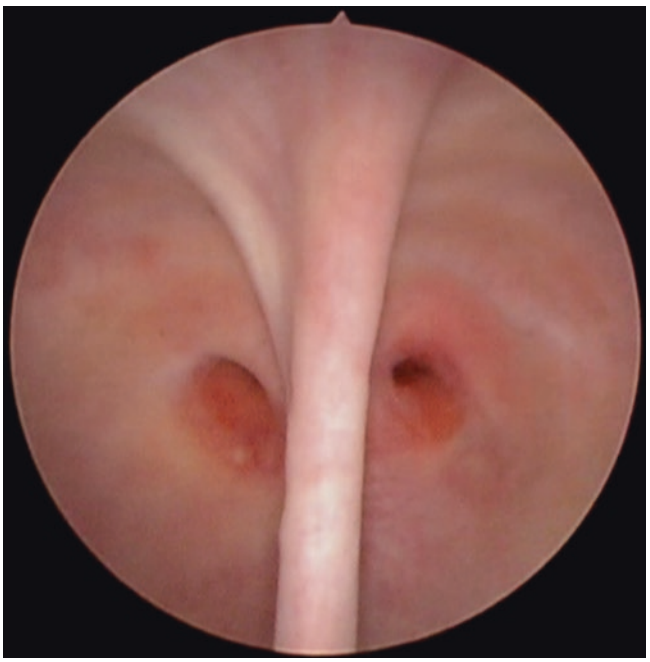

Fig. 1.11 Longitudinal non-obstructing vaginal septum, class V1 [5]. Two external cervical ostia are seen on either side of the septum

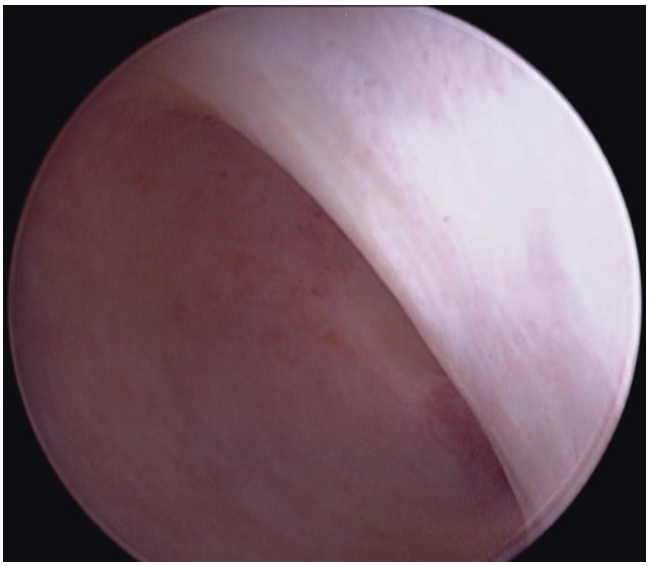

Fig. 1.12 Longitudinal obstructing vaginal septum, class V2 [5], in a case of didelphys uterus leading to an OHVIRA syndrome. Septum is obstructing the left hemi-vagina

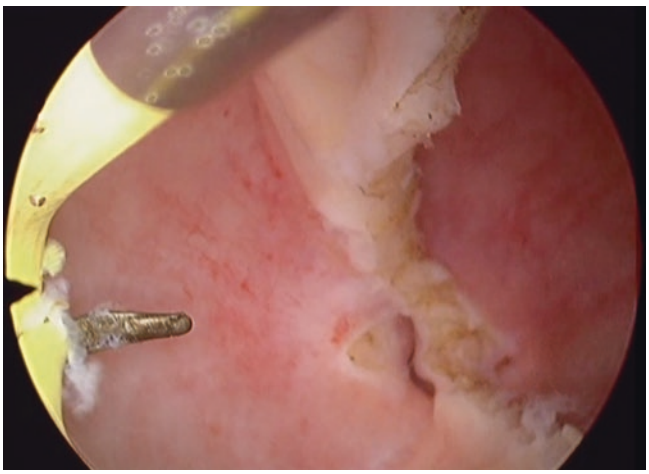

Fig. 1.13 Post-hysteroscopic correction of a longitudinal obstructing vaginal septum with the obstructed hemi-vagina now communicating with normal side

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Cyclic Endometrial Changes

2

Alfonso Arias and Alicia Úbeda

Although when students who learn hysteroscopy go in the look for organic and structural, benign, or malign pathology, this endoscopic technique allows much more. With the help of a video camera and increasing visual acuity (Figs. 2.1 and 2.2), hysteroscopy can describe either endometrium development or functional disturbances that may cause hypotrophy, hypertrophy, hyperplasia, and neoplasia [1]. This accuracy has shown to be higher than histologic examination, as the latter may miss nearly half of major intrauterine disorders [2].

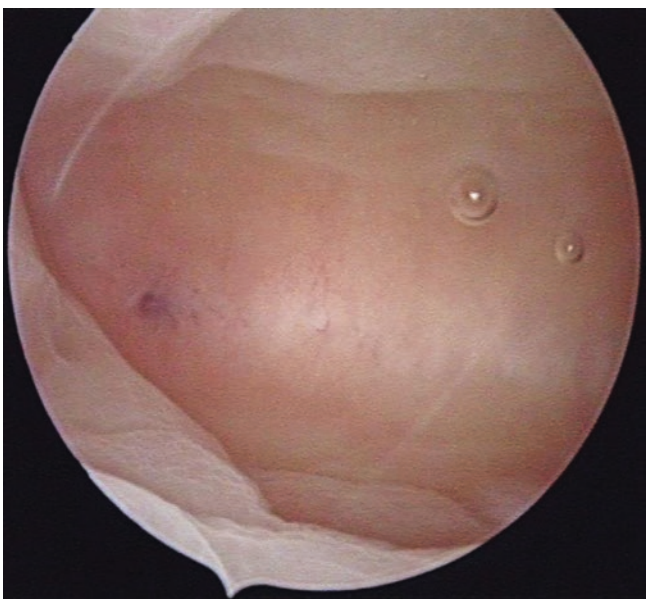

Fig. 2.1 Normal uterine cavity under fluid distention. Notice the right tubal ostium. Surrounding endometrium is in a secretory phase

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Endometrial changes are strongly related to ovarian stimulation in the absence of other external or internal stimuli. Hormone secretion is reflected in glandular and vascular changes, and therefore in visual appearance of this layer along a conventional cycle of 24–35 days. This evolution was yet first described in the early 1990s through CO_2 hysteroscopy [3] and strongly correlates with Netter's descriptions [4].

The endometrial tissue is made up of two layers: the basilar zone, which attaches the endometrium to the underlying myometrium, and the functional zone, which is the majority and the one that progressively changes under hormone influence. On the one hand, physiological changes in thickness and appearance are due to the ovarian hormones. On the other, other internal or external influences (hormonal, infectious, medication) may cause changes that will not be treated in this chapter.

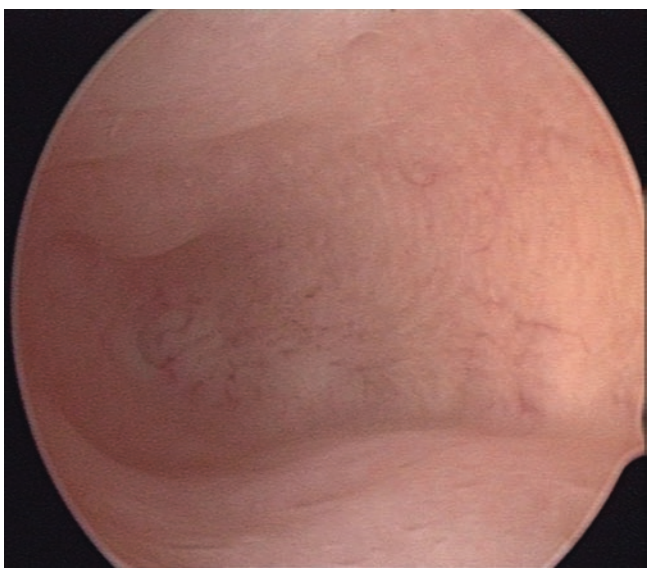

Fig. 2.2 Uterine right cornual region. Endometrium is in late secretory phase. Vessels start to be seen in the fundal area as menstrual phase is near to begin

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_2

This chapter describes the most frequent changes after endogenous ovarian stimulation image by image. The endometrial cycle starts with the detachment of its upper layer. Later, there are two main phases:

1. The proliferative phase, which is a period of tissue regeneration and mucosal growth (Figs. 2.3, 2.4, and 2.5): Under estrogen influence, both glands and vessels increase in number, size, and width towards the surface until ovulation (Fig. 2.6).
2. The secretory phase (Figs. 2.7, 2.8, 2.9, and 2.10), where the maturation occurs after progesterone effect, and glands increase in shape, come together, and hide vessels underneath.

Both stages are separated by ovulation and start of progesterone secretion. As long as hysteroscopic knowledge moves along, early and late half of each can also be differentiated. At the end, as hormone secretion stops from the ovaries, an ischemic phase starts and endometrial cycle ends [5].

Performance of hysteroscopy in the secretory phase shows two main advantages:

- The endometrial mucosa expresses the summing effect of both estrogen and progesterone influences, and allows the diagnosis of hypertrophic (Fig. 2.11) or hypotrophic (Fig. 2.12) endometrium.

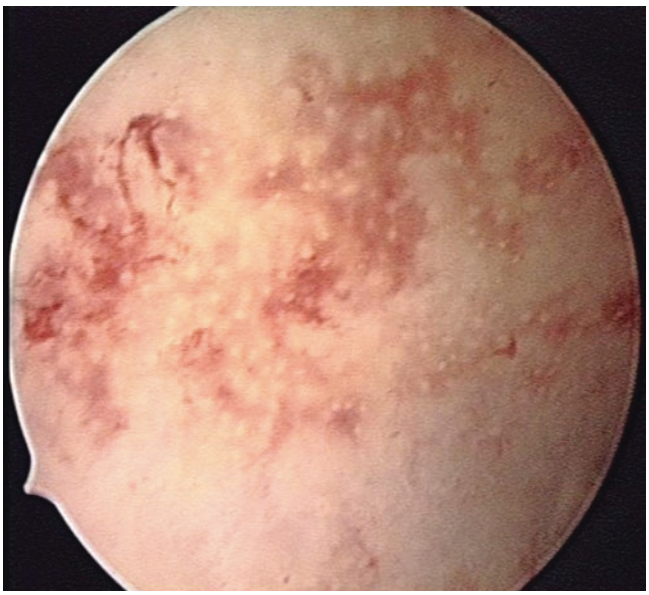

Fig. 2.3 Regenerative endometrium in the very early proliferative phase. Glands grow from the basal layer (out and inside the red plates) straight up to the surface and are seen as narrow white dots. Red areas belong to the basal layer which is still visible

- Endometritis will not be so easily missed because no red plates belonging to the proliferative phase will interact at the same time.

Final images of premenstrual (Figs. 2.13 and 2.14) and menstrual phases (Figs. 2.15 and 2.16) are infrequent but they show how the endometrium tears until being totally expelled.

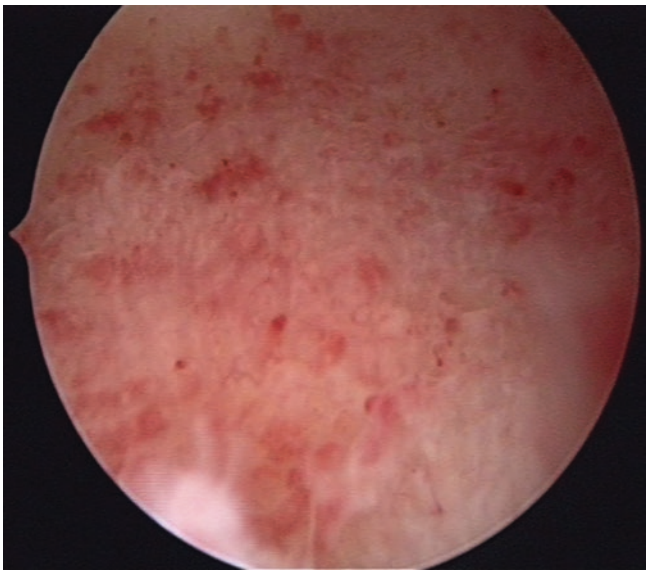

Fig. 2.4 Late proliferative phase: red plates are progressively hidden by glandular and vascular growth. Endometrial spiral arteries give a red color to the mucosa

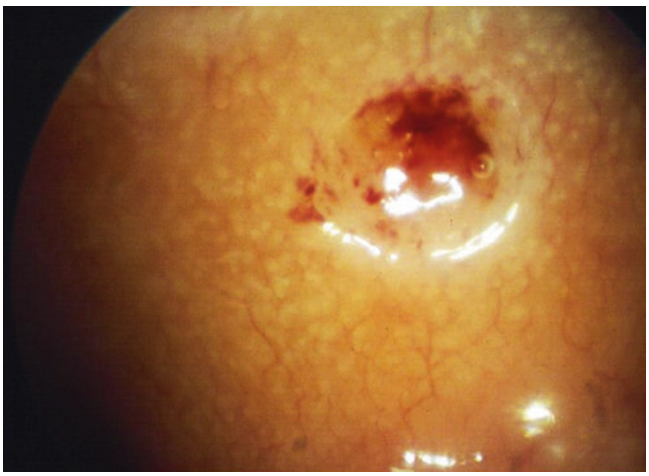

Fig. 2.5 Endometrial notch in the late proliferative phase. Small petechia appears under the hysteroscope's pressure. The procedure has been carried out under gas distention

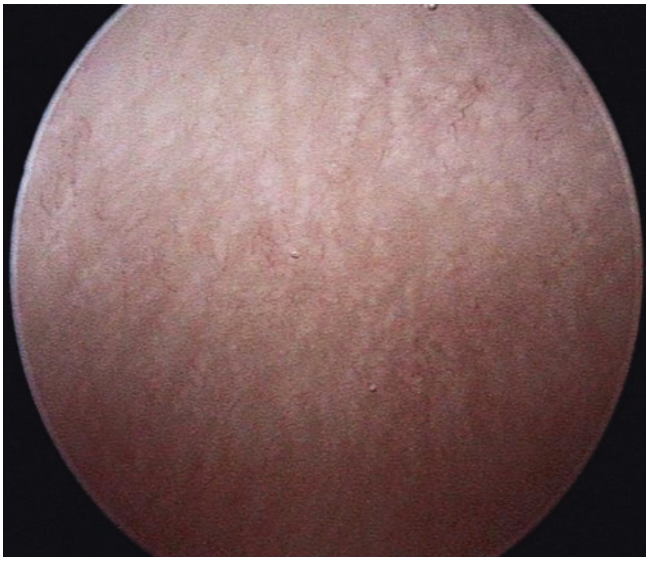

Fig. 2.6 The ovulatory phase: Under the progesterone stimuli glands end their growth and tend to come together, even though they are well distinguished. Different shapes are seen among white dots. Red color of the mucosa is substituted for a light yellow one

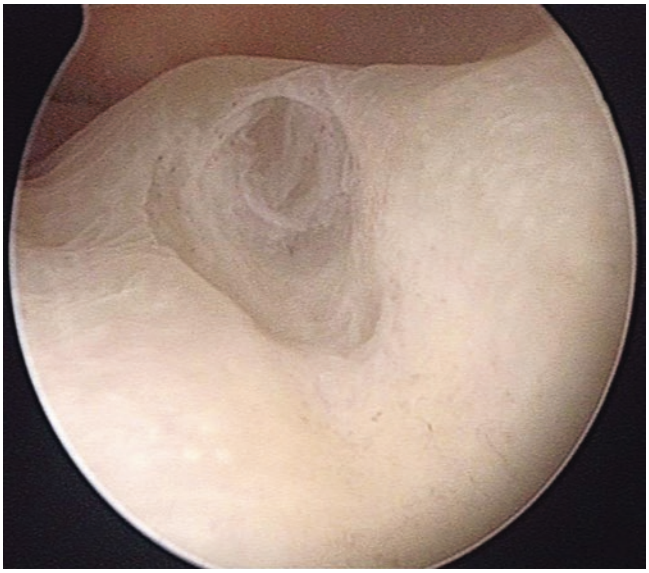

Fig. 2.8 Endometrial notch in the early secretory phase. Mucus secretion allows the hysteroscope's sinking as it is wide enough thanks to mucus secretion

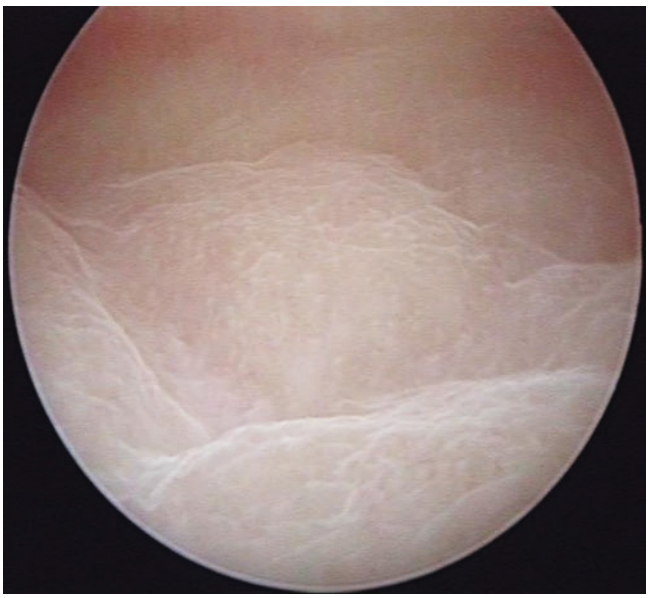

Fig. 2.7 Early secretory endometrium. A global whitish color starts to dominate after mucus glandular secretion in the mucosal surface. Still some glands are seen, though the majority have come together back to back. Vessels remain underneath and are no longer seen

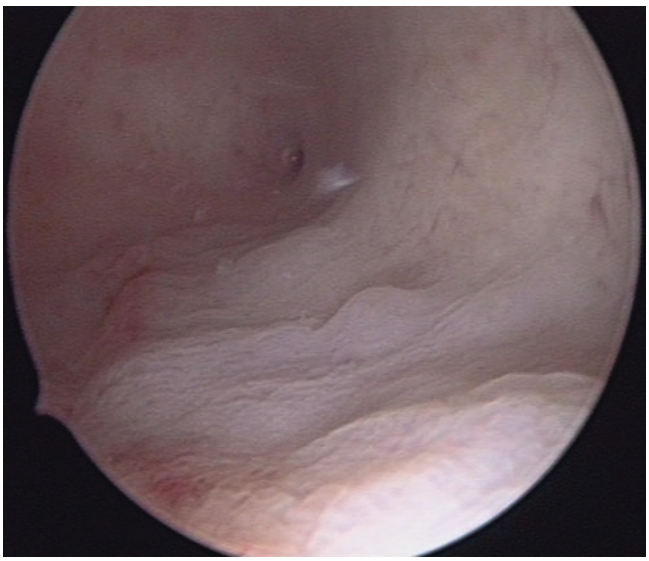

Fig. 2.9 Late secretory phase: Endometrium has flattened as glandular mucus has thickened. Color remains quite white. Endometrial glands are no longer seen as individuals

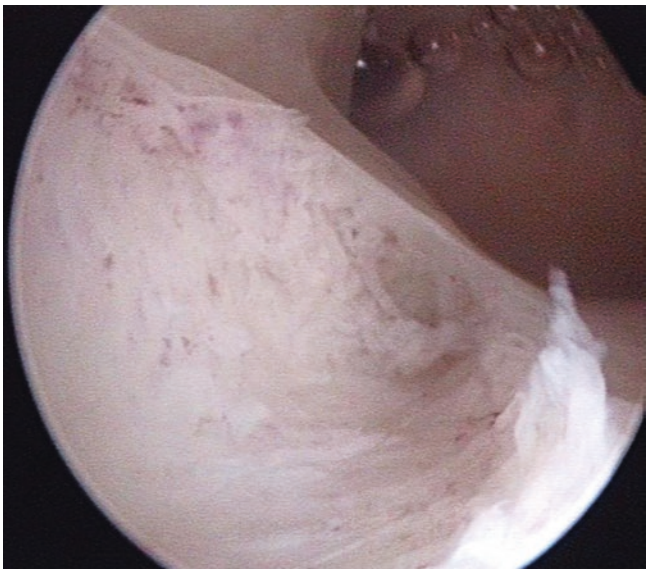

Fig. 2.10 Endometrial notch in the late secretory phase under the hysteroscope pressure. Thickening of the mucosa does not allow the hole sinking of the endoscope, as it is not as wide as in the early secretory phase

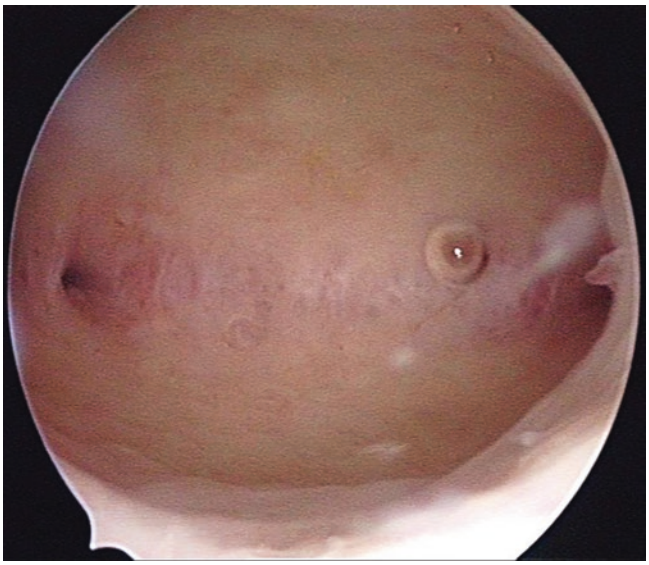

Fig. 2.12 Hypotrophic secretory endometrium in a 46-year-old woman. A decreased influence of both estrogens and progesterone makes the mucosa thinner compared to that in younger women. Myometrial fibers are seen in the fundal area

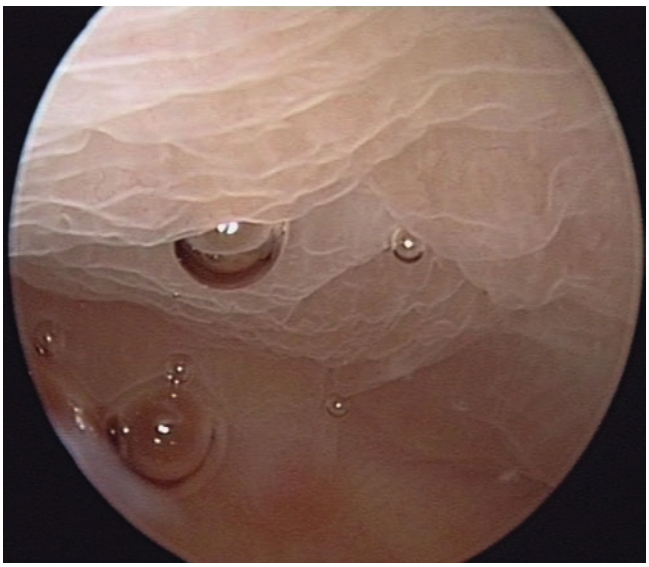

Fig. 2.11 Light endometrial hypertrophy under a disbalanced influence of estrogens over progesterone in the mid-secretory phase

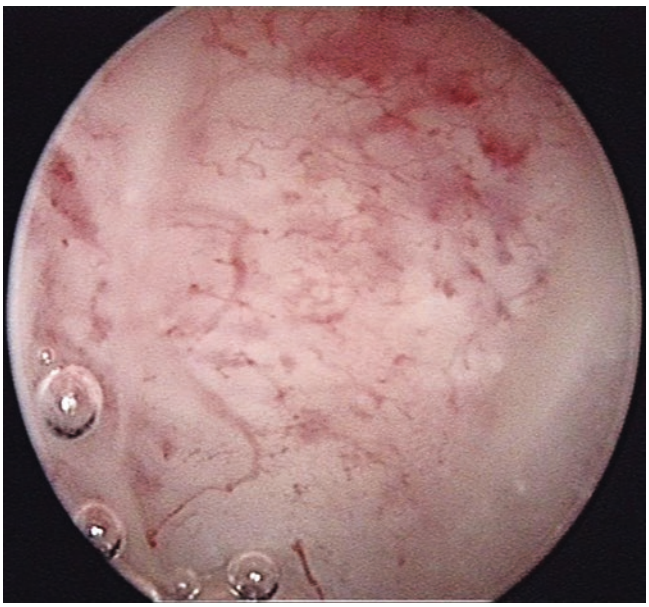

Fig. 2.13 Early premenstrual phase. Short vessels start to appear in the endometrial surface

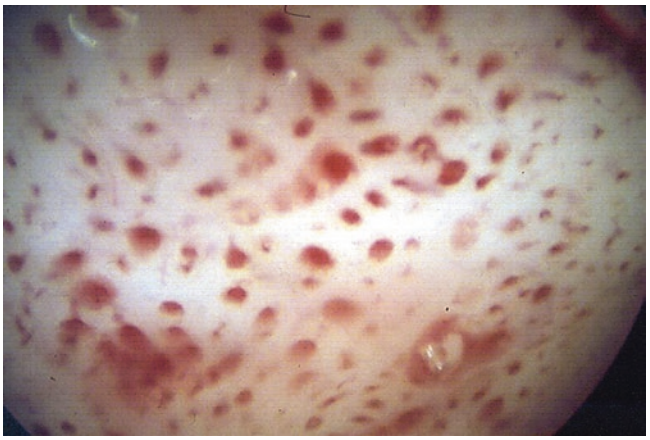

Fig. 2.14 Early menstrual phase. The mucosa starts its tearing as little bleeding holes. This image is not often seen. This hysteroscopy was carried out under CO_2 distention

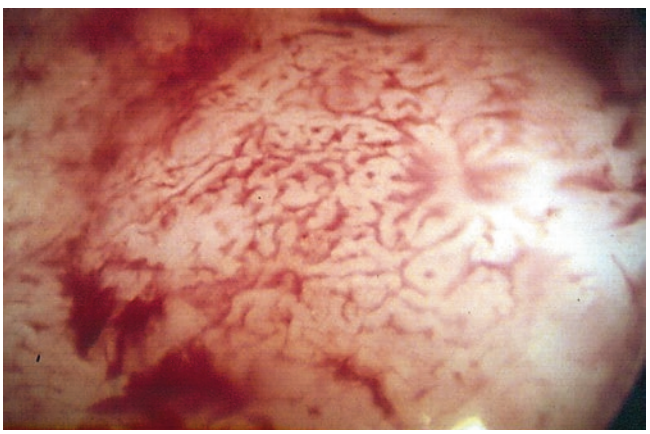

Fig. 2.15 Exceptional image of the immediate beginning of the menstrual phase. Tearing of the functional mucosa starts to take off from the basal layer and torn vessels clearly start to bleed

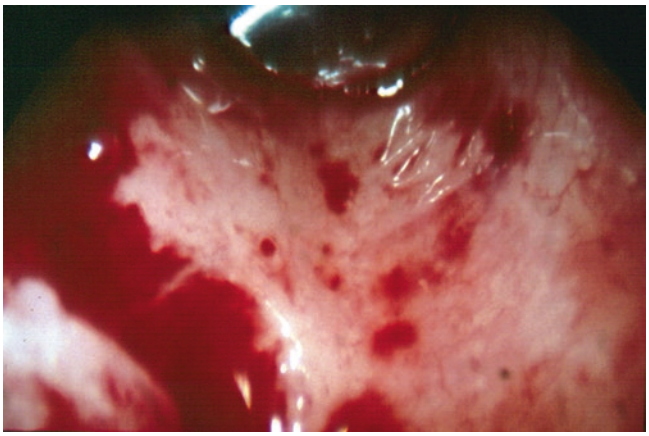

Fig. 2.16 Full menstrual phase. This image has been taken under CO_2 distention. Endometrial grooves result from the partially expelled upper mucosa

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The Atrophic Endometrium

3

Nash S. Moawad, Alejandro M. Gonzalez, and Santiago Artazcoz

3.1 Introduction

The endometrium is the hormonally responsive glandular tissue lining the uterine cavity. This tissue consists of:

1. Epithelium (endometrial glands)
2. Stroma (endometrial stroma)

The structure and activity of a functional endometrium reflect the pattern of ovarian hormone secretion. The histologic types of glandular cells are columnar or cuboid. The endometrium undergoes regular growth and maturation throughout the menstrual (endometrial) cycle, corresponding to the proliferative effects of estrogen and secretory effects of progesterone produced by the ovary during the hormonal (ovarian) cycle. In the absence of pregnancy, shedding of the thickened, vascular endometrial lining occurs in the form of a menstrual cycle, leading to a thin endometrium, followed by regeneration.

The endometrial tissue becomes atrophic after menopause as a result of cessation of ovulation and ovarian estrogen and progesterone secretion. At this time, there is loss of the functional layer and the endometrial glands take on a simple tubular or low cuboidal, often cystic, form, showing neither proliferative nor secretory activity, whereas the endometrial stroma becomes fibrotic.

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The diameter of the glands usually is 0.1 mm and the thickness of the endometrium on transvaginal ultrasound is less than 4 mm.

Microscopic examination shows the following:

Glands: small columnar cells:

- Moderate quantity of eosinophilic cytoplasm
- Ovoid (palisaded) nuclei, more or less nuclear pseudostratification
- No mitoses

Architecture:

- Cystic dilation

In the absence of sufficient estrogenic stimulation, the epithelium becomes quiescent and can appear as either weakly proliferative (inactive) or atrophic.

Weakly proliferative endometrium shows a pattern intermediate between normal proliferative and atrophic. The epithelium is columnar, with only a minor degree of pseudostratification. The nuclear chromatin is dense. Atrophic endometrial epithelium is low cuboidal to flattened, with a single row of dense nuclei. Mitotic activity is absent.

There are four histological types of atrophic endometrium, atrophic inactive, atrophic/weakly proliferative (non-inactive), mixed (inactive and non-inactive), and cystic atrophic [1, 2].

1. Atrophic and inactive endometria are defined as those deprived of functionalis and consisting exclusively of thin basalis with a few narrow tubular glands lined by cuboidal indeterminate epithelium showing neither proliferative nor secretory activity.
2. Atrophic/weakly proliferative (atrophic non-inactive) endometria are defined by the following criteria:
   (a) Shallow endometrium 2.2 mm thick (mean 2.2, range 1.0–3.5 mm) with the loss of distinction between the basal and functional layer

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_3

(b) Proliferative-type epithelial glands, somewhat tortuous, with tall columnar pseudostratified epithelium, oval nuclei, and very infrequent mitoses
(c) A dense fibrotic endometrial stroma devoid of mitoses
3. Mixed: The mixed form of endometrium is defined as atrophic and inactive endometria showing focal areas of weakly proliferative glands.
4. Cystic atrophic endometrium.

Often, atrophic endometrium has cystically dilated glands. These may be the atrophic variants of cyclically dilated glands that are seen in the lower functionalis in women aged 35 years and above. Cystically dilated glands also are seen in cystic glandular hyperplasia with retrogressive atrophy. In this case the endometrial mucosa retains the thickness of an otherwise active hyperplasia, but the glandular epithelium is atrophic and the stroma is collagenized and no mitotic figures are seen. A third explanation is that fibrosis of the stroma blocks the glands that then become distended.

Cystic endometrial atrophy is a benign process that can occur as part of tamoxifen-associated endometrial changes. It is diagnosed histologically when multiple cystic spaces (dilated glands) lined with atrophic epithelium are present within a dense fibrous stroma. It is an unusual hysteroscopic finding.

At hysteroscopy, the endometrium appears white but hypervascularized, with scattered protuberances. This "tamoxifen-like" mucosa can be seen as early as 6 months after the start of tamoxifen therapy. At histopathologic examination, these protuberances are identified as cystic glandular dilatation [3, 4].

This condition is benign and is not associated with an increased risk of either endometrial adenocarcinoma or endometrial hyperplasia.

While atrophic glands are characteristic of premenopausal patients taking exogenous hormones, atrophy in any other setting in a premenopausal woman is an unexpected finding and its significance is not well understood.

Why is it so important to take this condition into account?

The most frequent cause of postmenopausal bleeding is endometrial atrophy, found in approximately 45–50% of the patients. The exact cause of bleeding from the atrophic endometrium is not known. It is postulated to be due to anatomic vascular variations or local abnormal hemostatic mechanisms. Thin-walled veins, and thin fragile stromal support of these superficial vessels [1].

An Italian prospective study that includes 18 centers and 930 patients showed that an endometrial thickness of ≤4.0 mm safely predicts endometrial atrophy and justifies expectant management of patients with postmenopausal bleeding, as long as the patient understands the need for proper follow-up should bleeding persist, recur, or worsen [5].

The cutoff of 4 mm is important for general gynecologists and hysteroscopic surgeons because sometimes with thin endometrium in ultrasound it is not necessary to perform diagnostic hysteroscopy or endometrial biopsy.

It is important for hysteroscopic surgeons to recognize the variable patterns of the normal atrophic endometrium, in order to direct guided biopsies and proper management of abnormal endometrial lesions, while avoiding overtreatment and unnecessary procedures when normal atrophic patterns are noted and confirmed by pathologic examination when needed [6, 7] (Figs. 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 3.10, 3.11, 3.12, 3.13, 3.14, 3.15, 3.16, 3.17, 3.18, 3.19, 3.20, 3.21, 3.22, 3.23, 3.24, 3.25, 3.26, 3.27, 3.28, 3.29, 3.30, 3.31, 3.32, 3.33, 3.34, 3.35, 3.36, 3.37, 3.38, 3.39, 3.40, and 3.41).

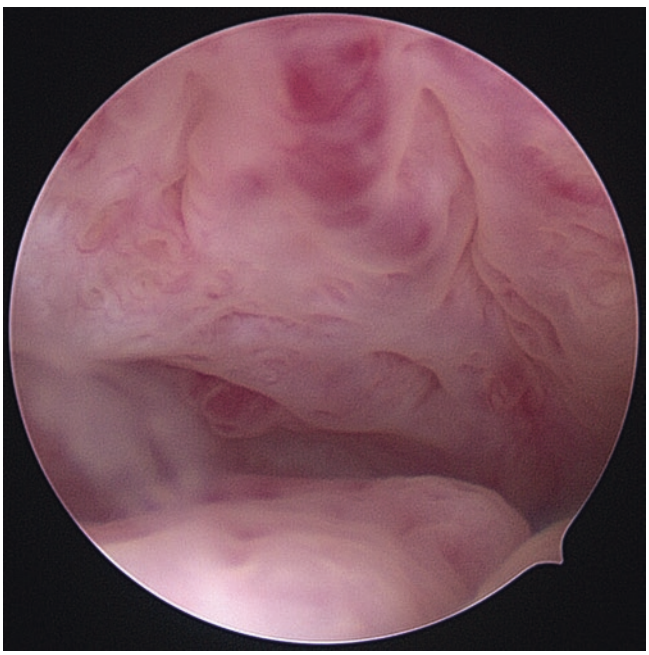


Fig. 3.1 Abnormally thickened postmenopausal endometrium in a patient with a history of endometrial ablation

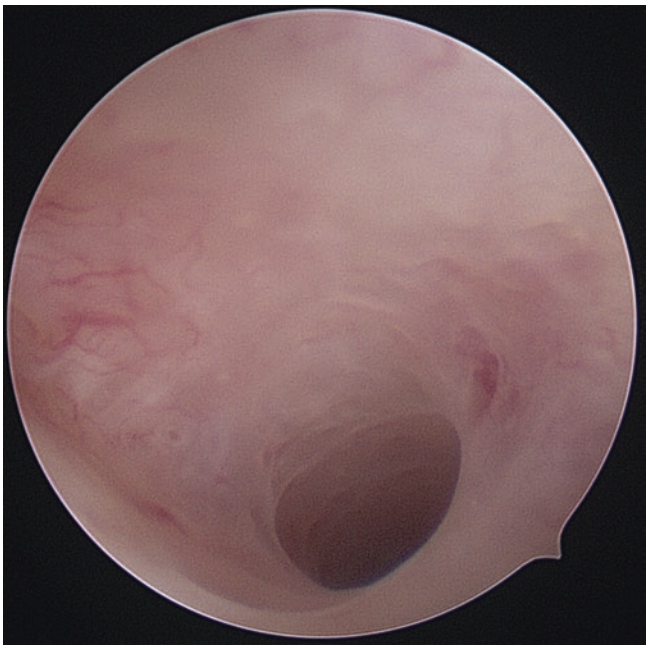
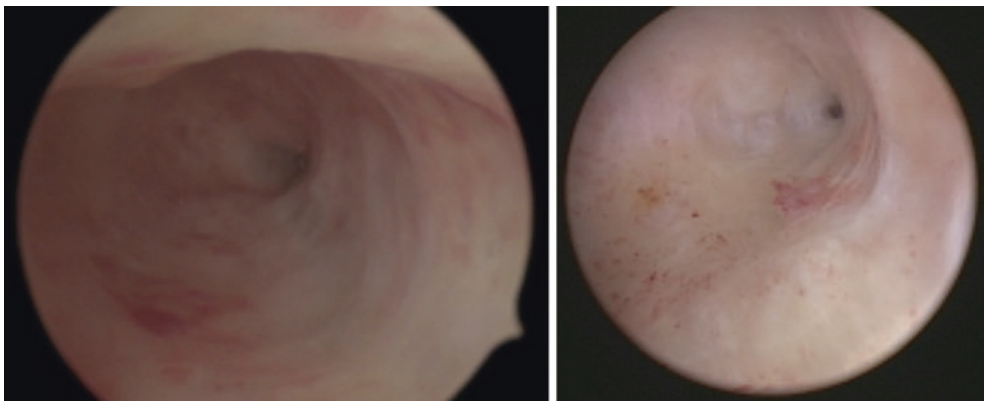


Fig 3.2 Atrophic cervical canal with cervical stenosis

Fig. 3.3 Atrophic cervical canal, status post-cervical dilation of cervical stenosis. The typical features of the cervical canal are absent

Fig. 3.4 Pale atrophic endometrium of the left cornual region; tubal ostium noted



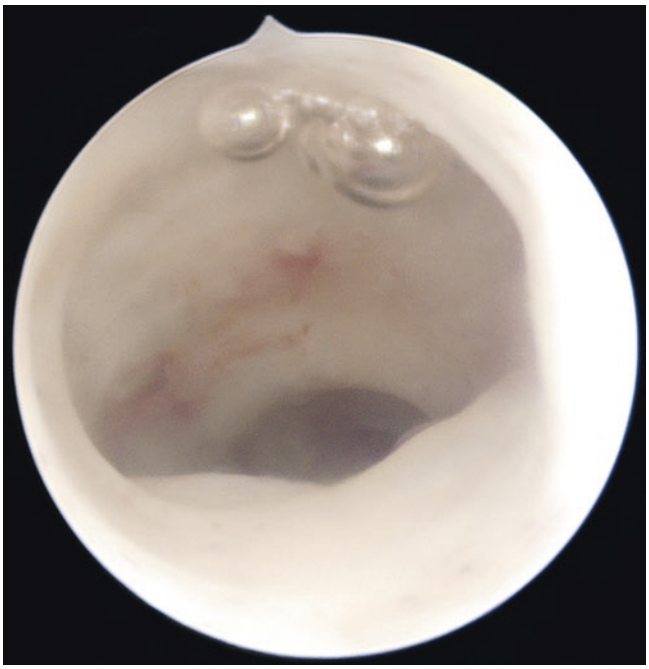


Fig. 3.5 Pale atrophic endometrium

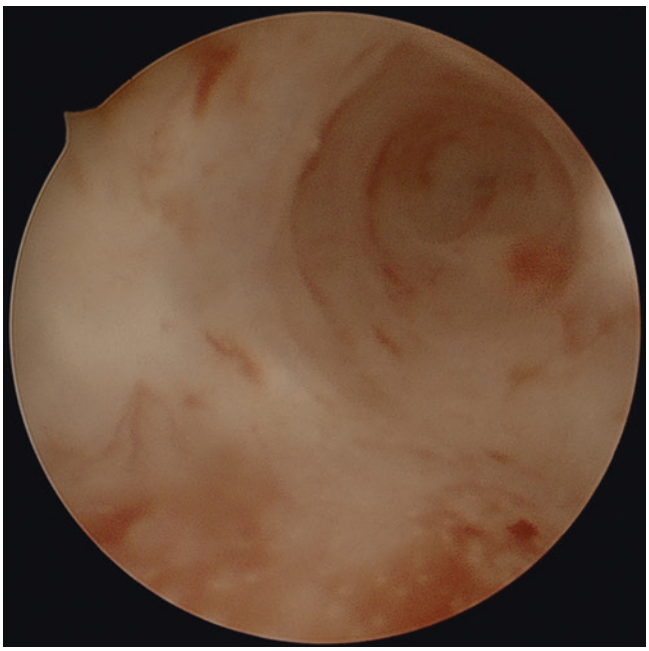
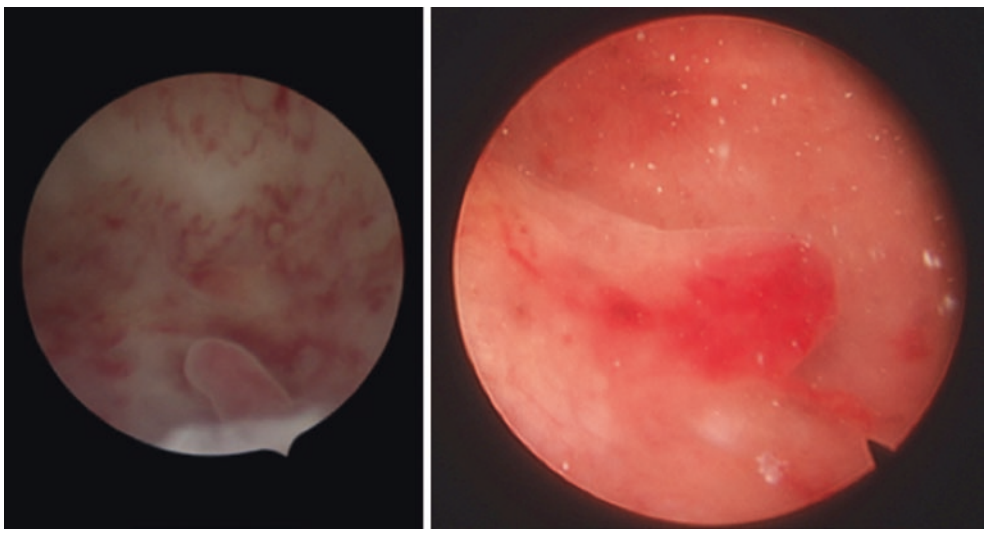


Fig. 3.7 Pale atrophic endometrium with subtle cystic changes and fibrotic stroma; Asherman's following endometrial ablation

Fig. 3.6 Atrophic endometrium with subendometrial vasculature and a micropolyp



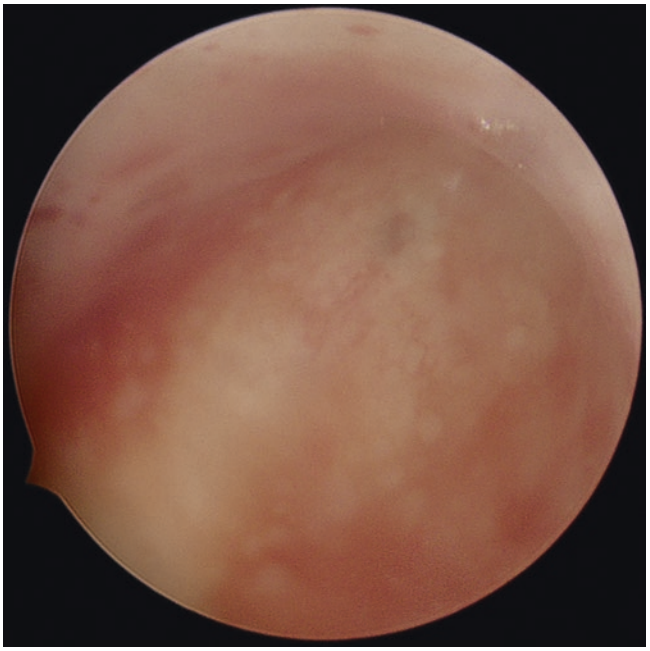


Fig. 3.8 Cystic changes in a smooth atrophic endometrium of the left cornual region and tubal ostium

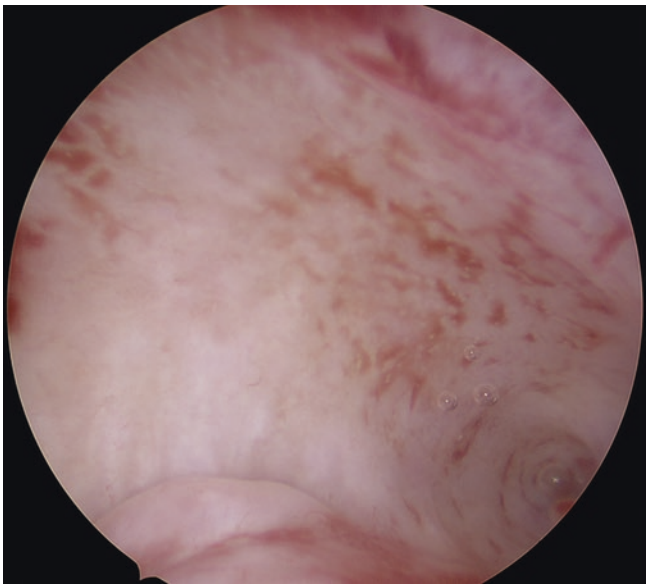


Fig. 3.10 Atrophic endometrium, status post-endometrial ablation

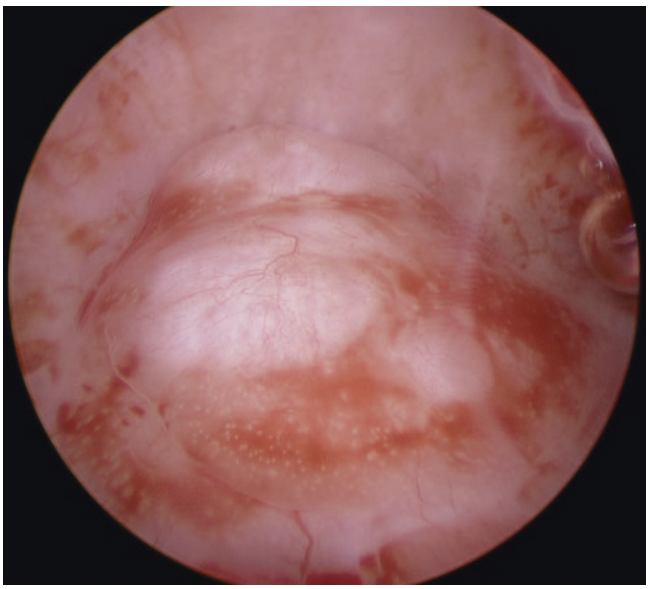


Fig. 3.9 Atrophic endometrium overlying a type 2 submucosal fibroid and subendometrial vasculature

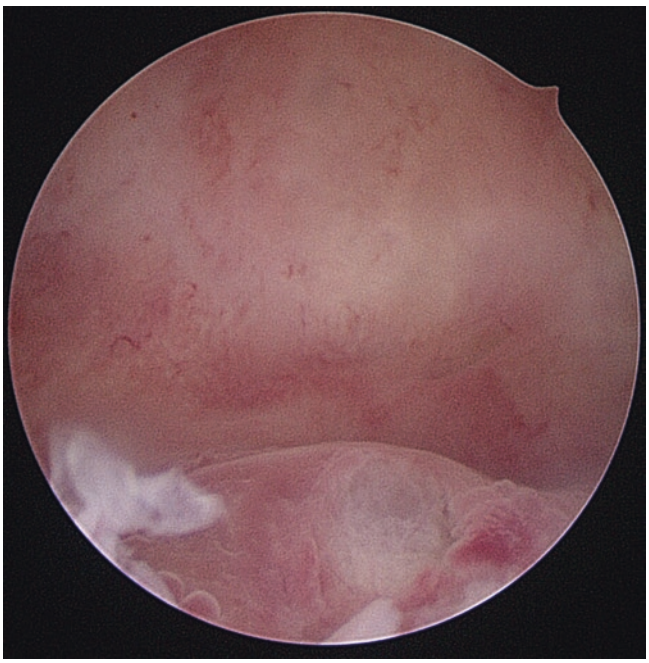


Fig. 3.11 Atrophic endometrium with a posterior sessile polyp

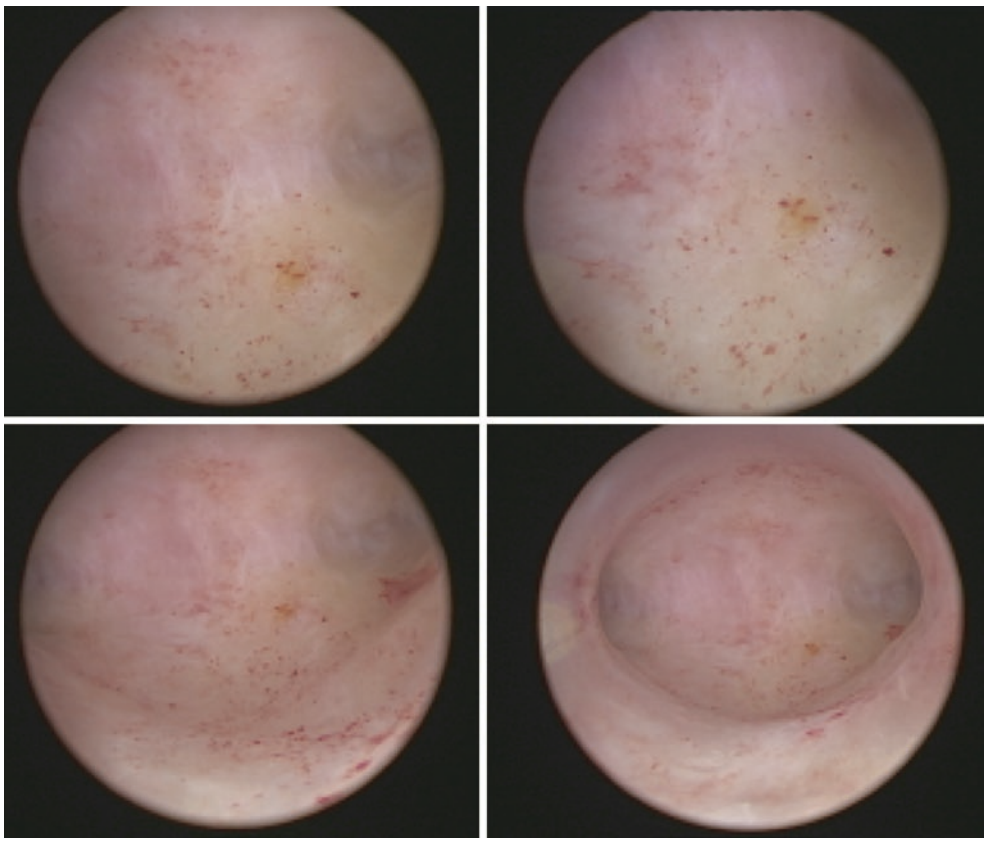


Fig. 3.12 Typical thin atrophic endometrium with petechial hemorrhages in the uterine fundus

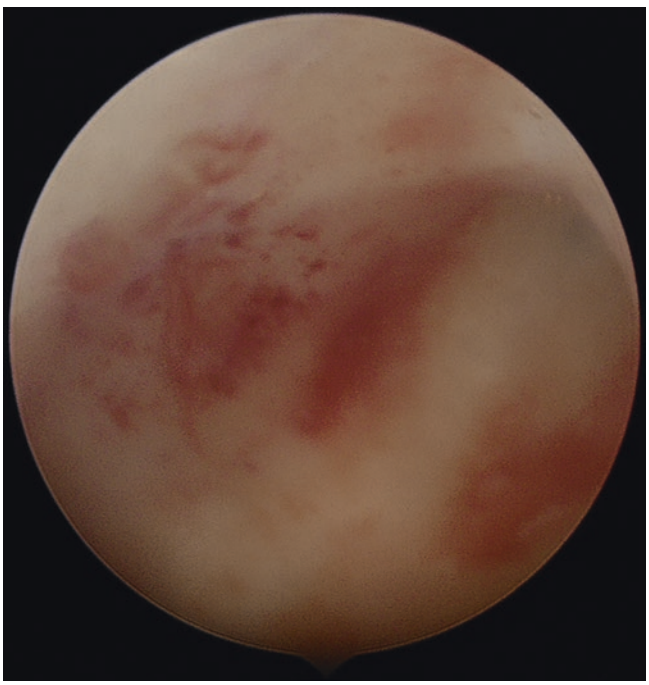


Fig. 3.13 Atrophic endometrium with subendometrial hemorrhage

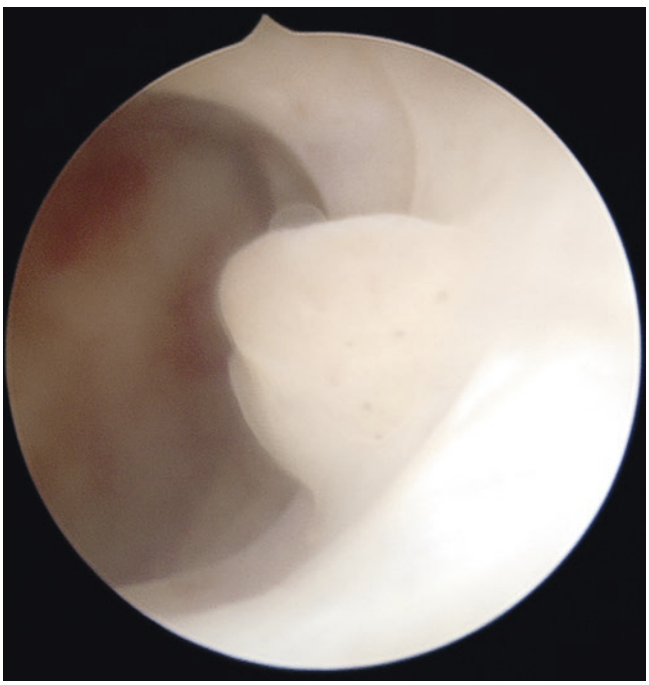


Fig. 3.14 Atrophic micropolyp

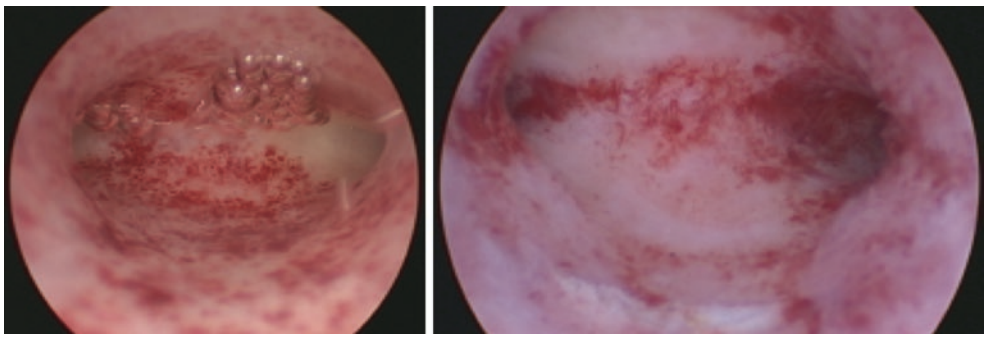


Fig. 3.15 Panoramic view of a small atrophic cavity with subendometrial petechiae and no focal lesions

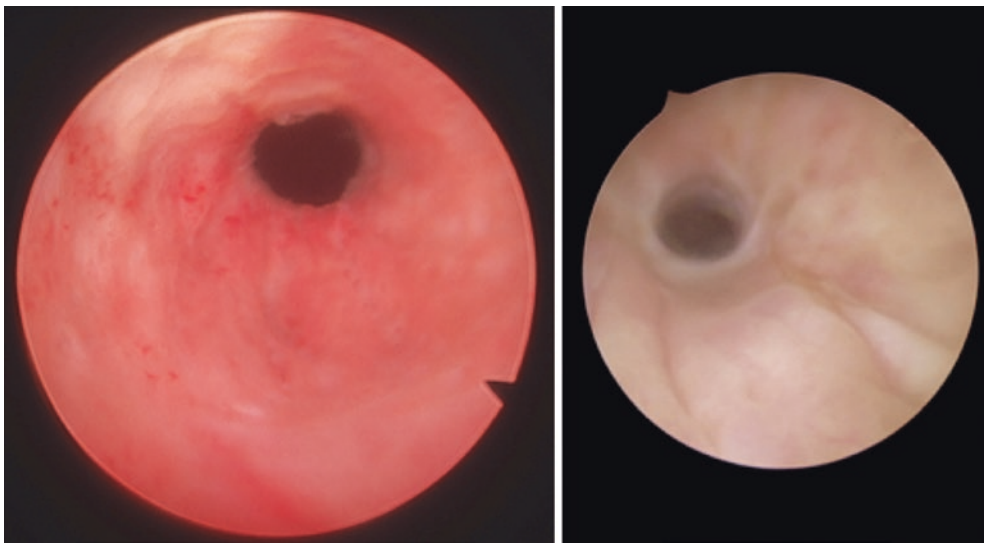


Fig. 3.16 Thin atrophic cervical canal with stenosis of the internal os; a common finding in postmenopausal women

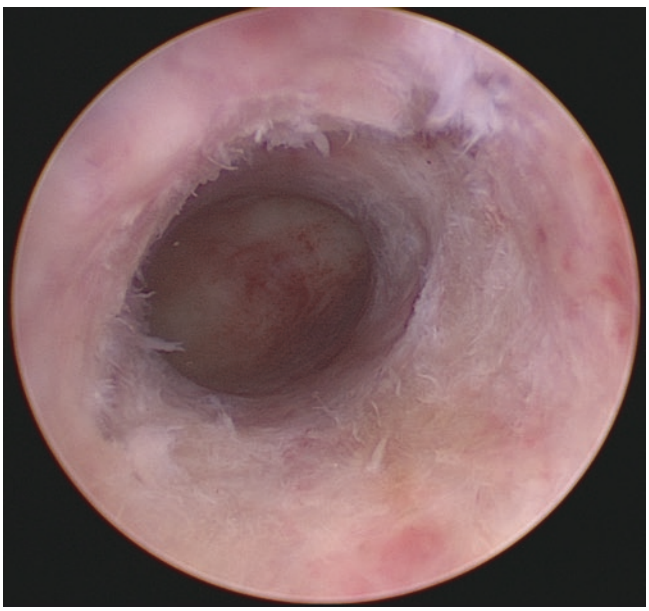


Fig. 3.17 Endocervical fibrotic changes in a small atrophic uterus

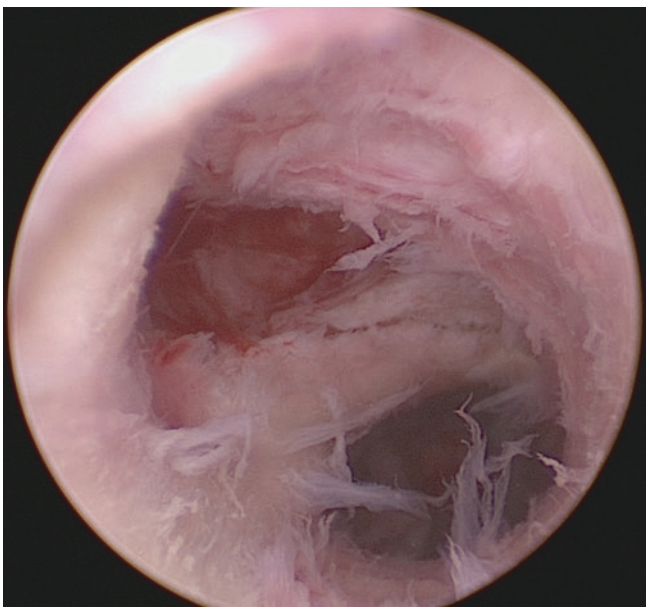


Fig. 3.18 False track in a patient with atrophic endometrium and cervical stenosis

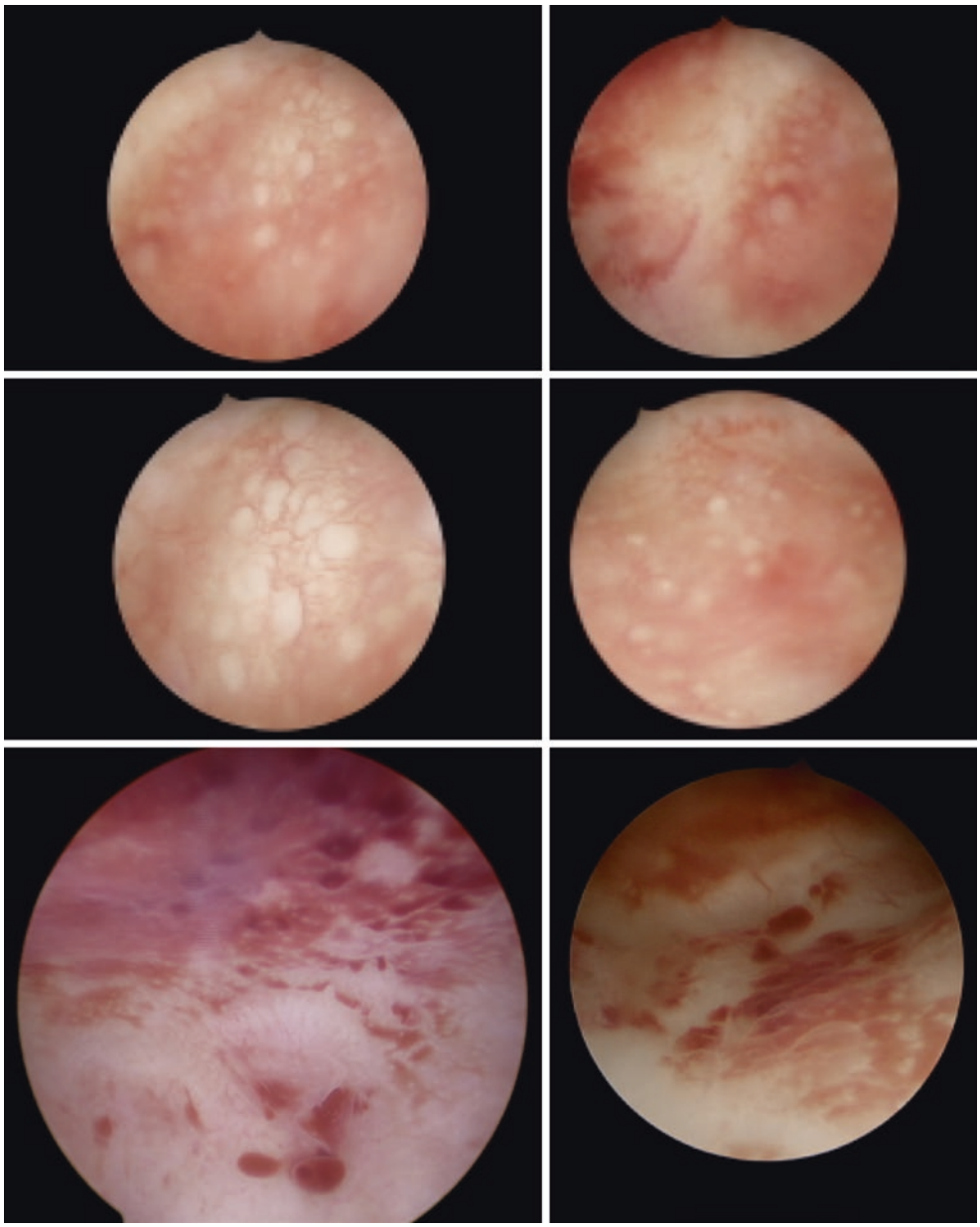


Fig. 3.19 Cystic changes in a background of atrophic endometrium

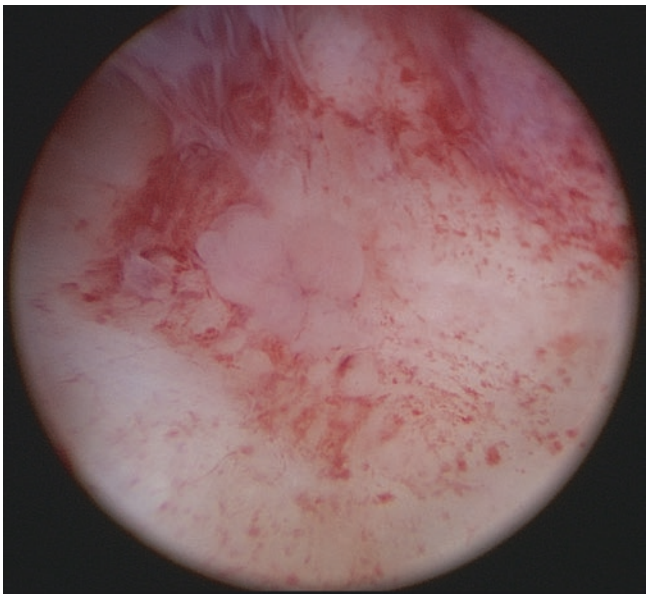


Fig. 3.20 Cystic changes and petechial hemorrhage in atrophic endometrium

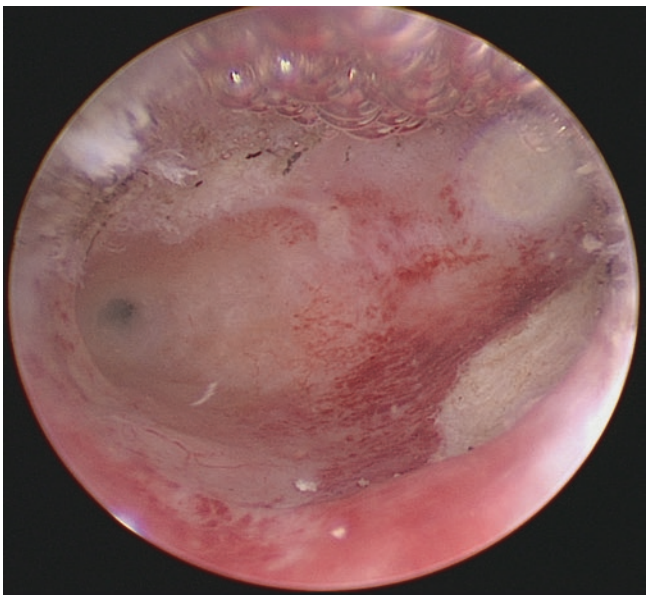


Fig. 3.21 Atrophic endometrium with hysteroscopically guided biopsies

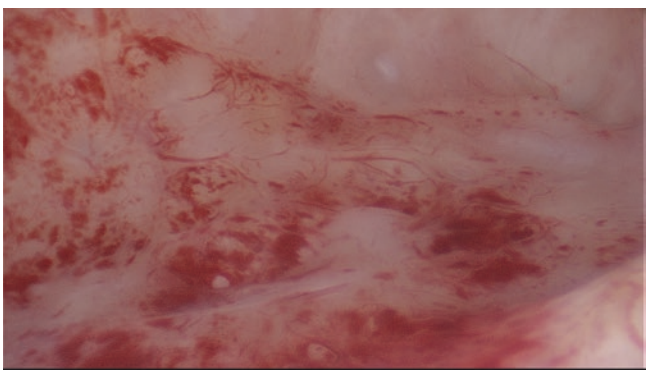
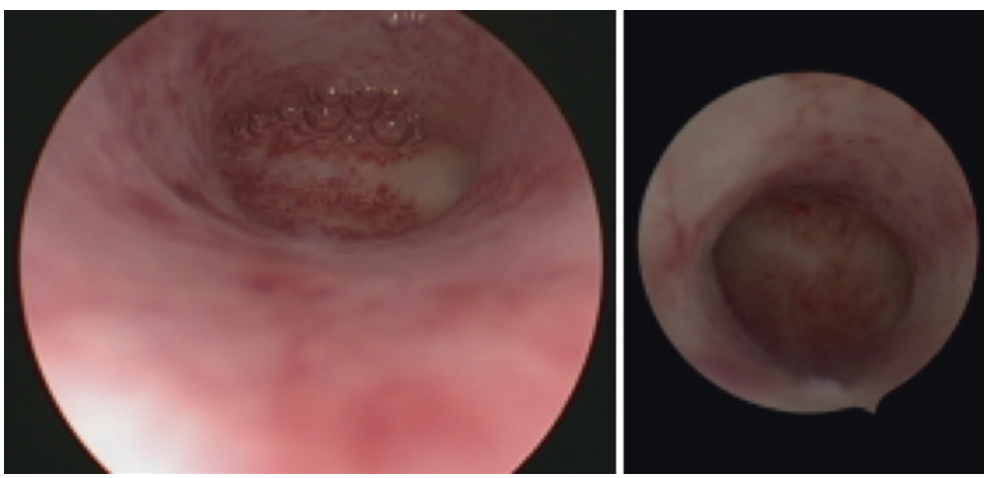


Fig. 3.22 Irregular subendometrial vessels

Fig. 3.23 Small postmenopausal endometrial cavity with atrophic endometrium



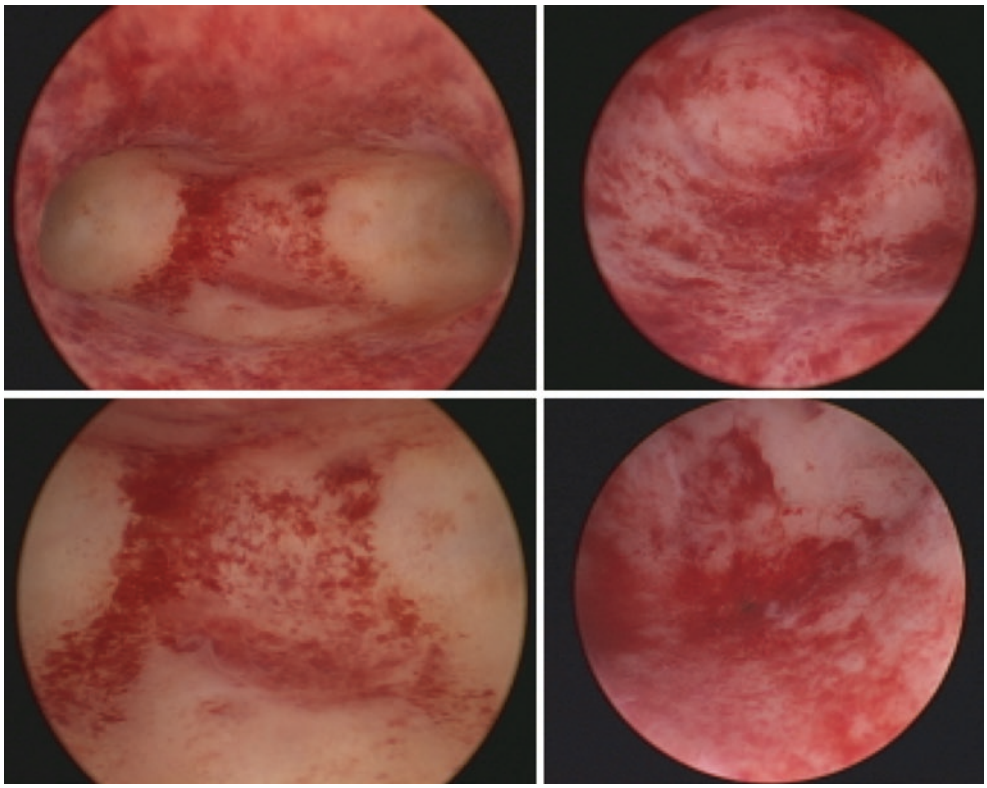


Fig. 3.24 Subendothelial vascular pattern is frequently apparent due to the thin translucent atrophic endometrium

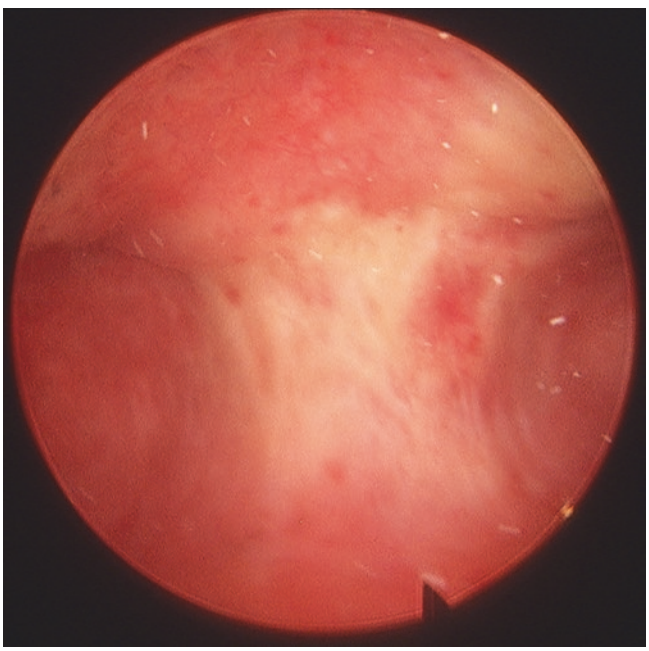


Fig. 3.25 Atrophic endometrial lining in a subseptate uterus

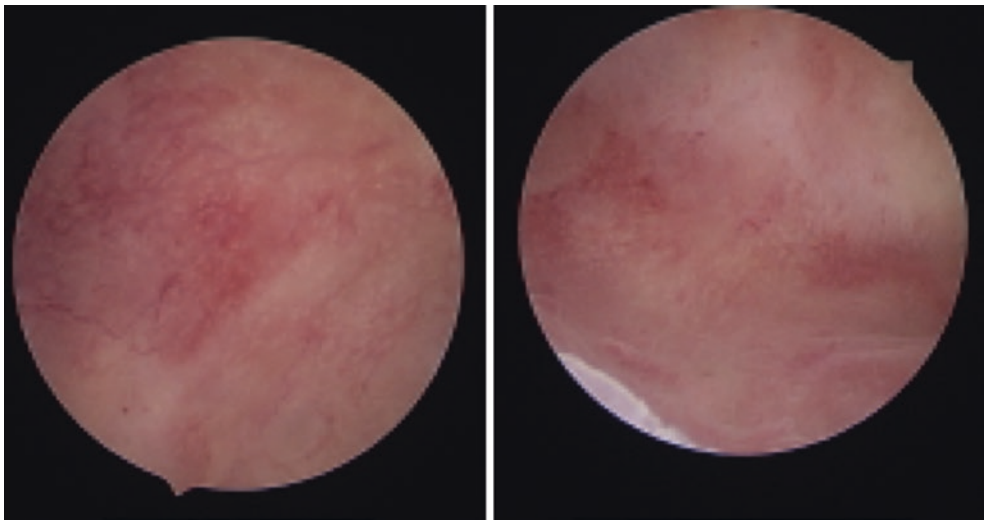


Fig. 3.26 Thin atrophic endometrium with speckled white appearance

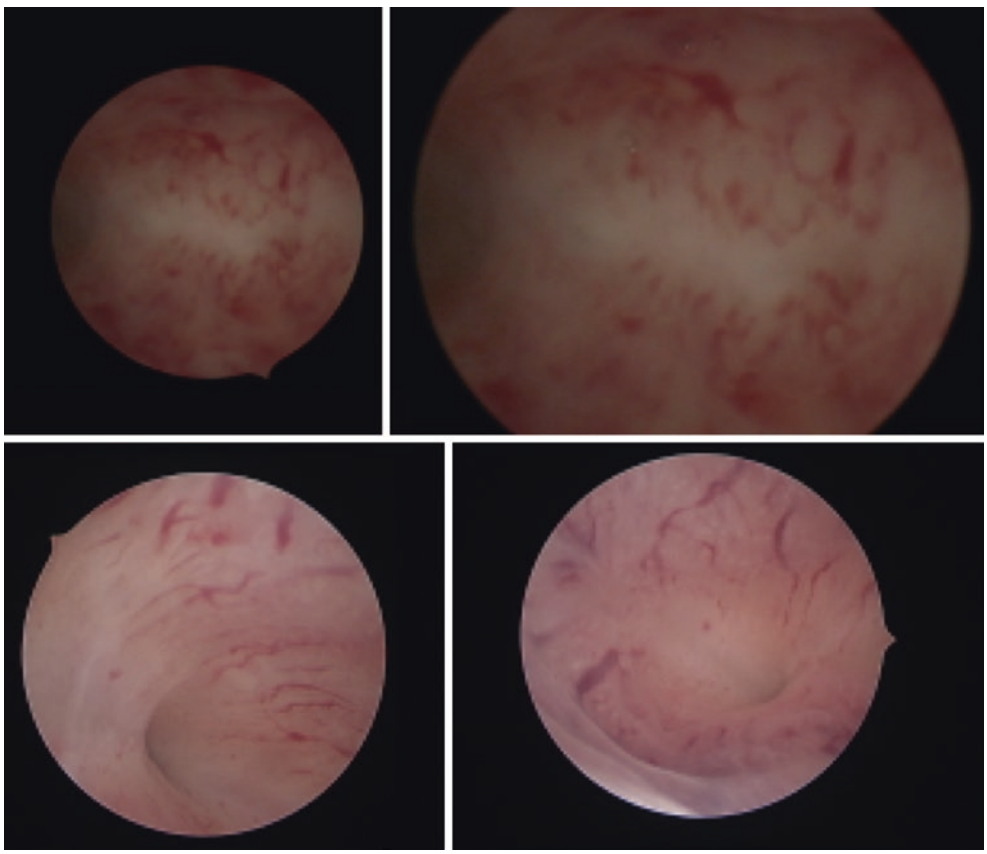


Fig. 3.27 Subendometrial vascular pattern in a postmenopausal patient with a history of endometrial ablation

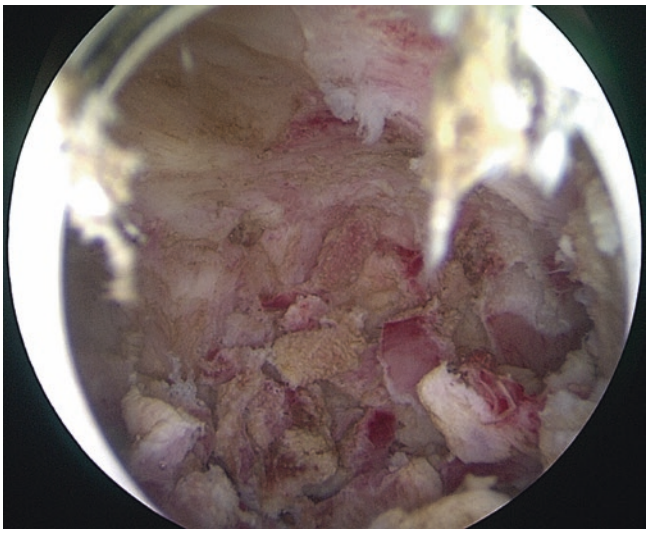


Fig. 3.28 Endomyometrial resection for recurrent postmenopausal bleeding in a patient with a history of endometrial ablation and benign pathology

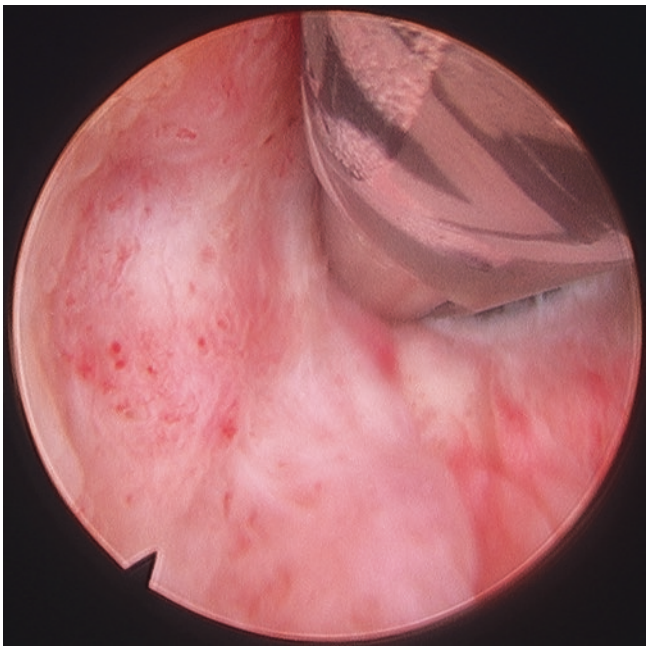


Fig. 3.30 Visual D&C using the hysteroscopic morcellator in a postmenopausal obese patient with a history of multiple C-sections and an irregular stenotic cervix

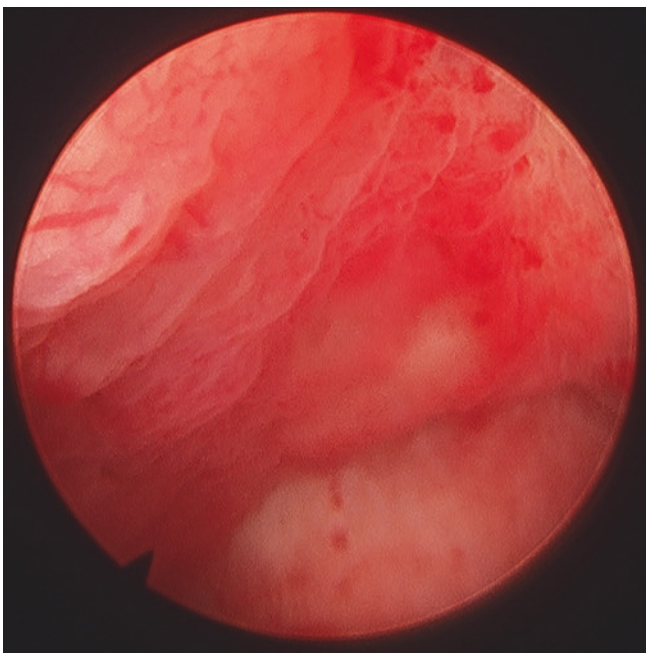


Fig. 3.29 Unexpected thick secretory endometrium in a postmenopausal patient

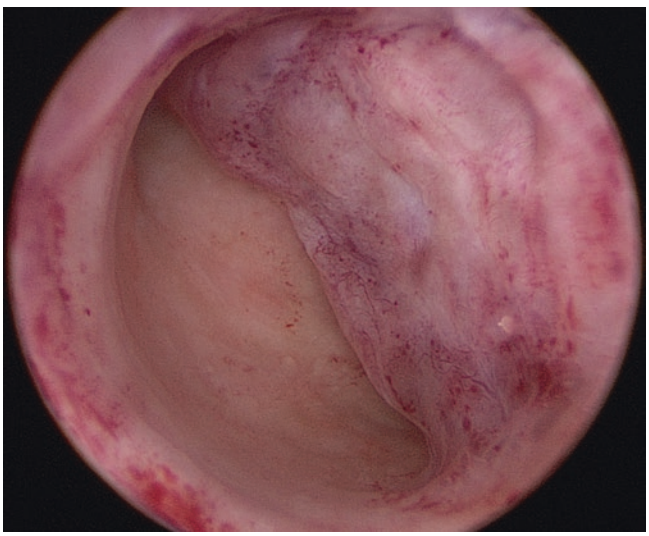


Fig. 3.31 Atrophic endometrium with a large lateral polyp

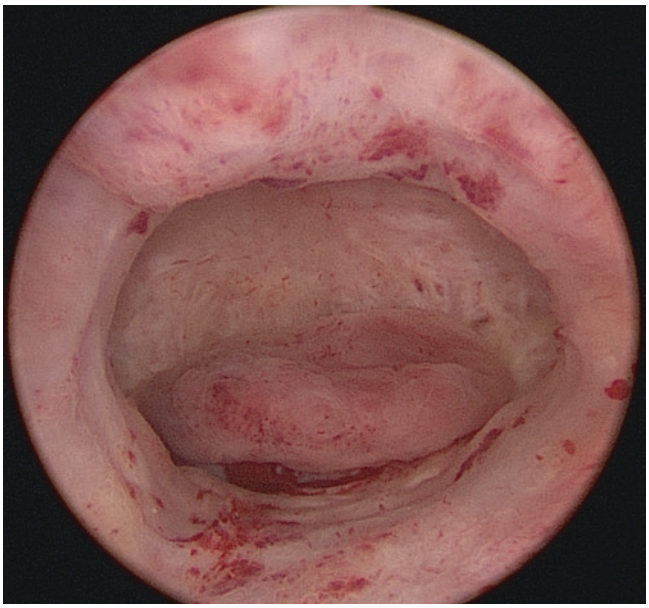
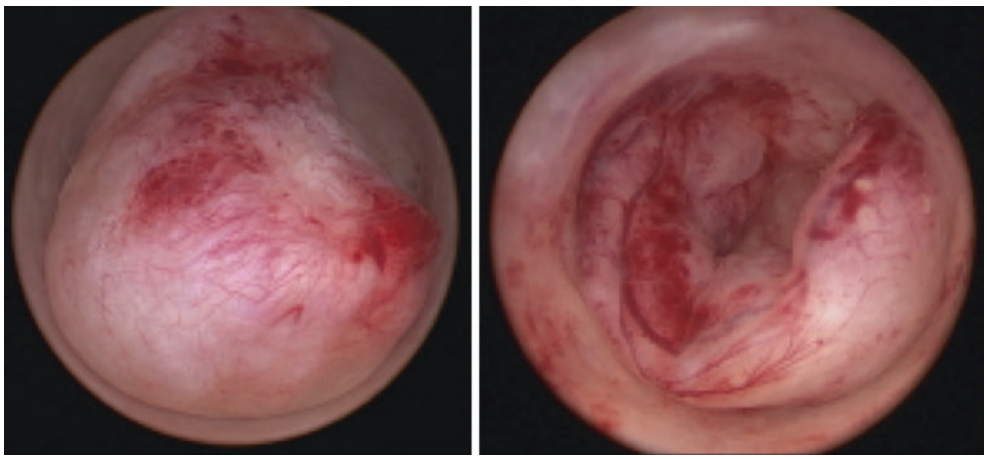


Fig. 3.32 Hyperplastic polyp in a background of atrophic endometrium

Fig. 3.33 Large polyps with irregular vessels in a background of atrophic endometrium



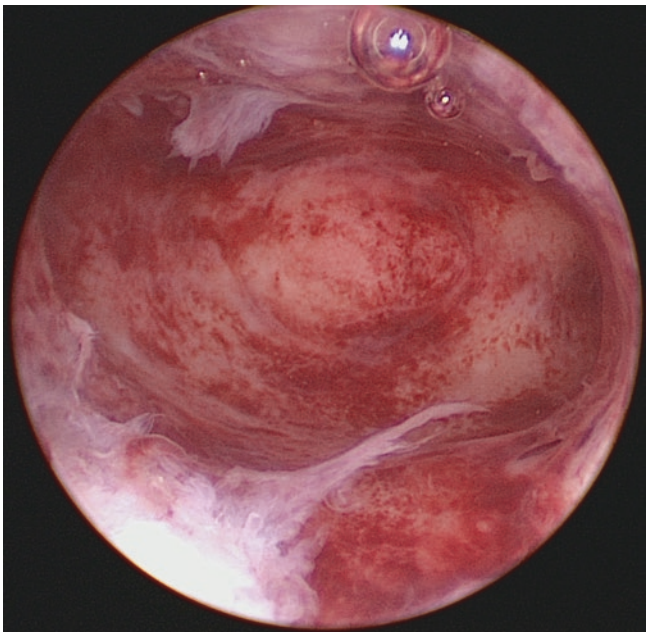


Fig. 3.34 Atrophic endometrium with thin intrauterine synechiae

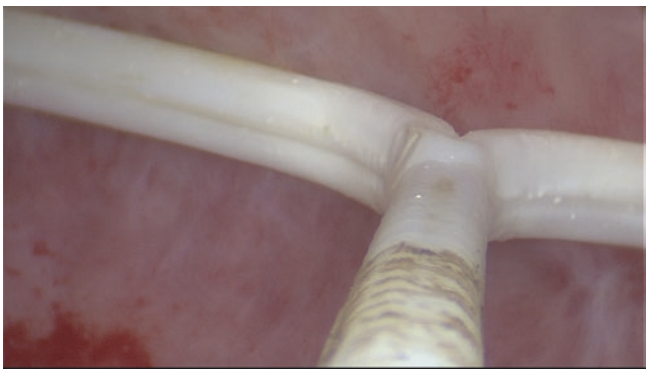


Fig. 3.35 Intrauterine device with surrounding endometrial atrophic changes

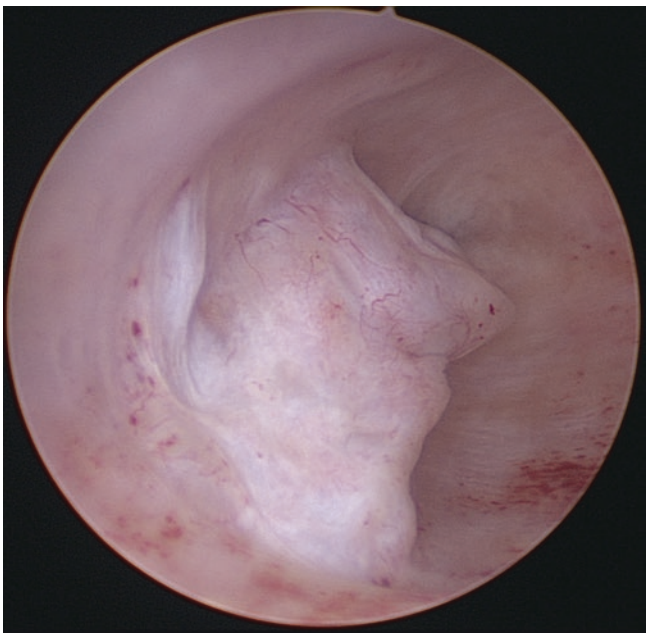


Fig. 3.36 Atrophic endometrium with a pale fibrotic polyp

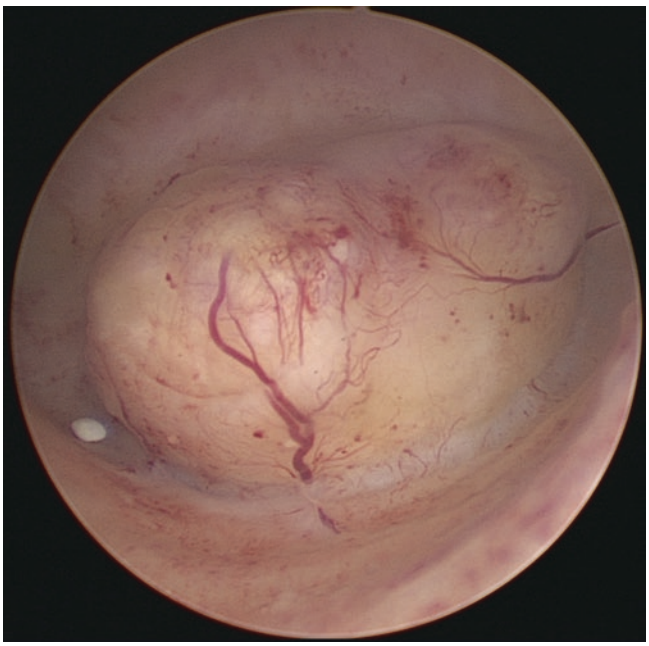


Fig. 3.37 Atrophic endometrium with superficial vessels overlying a type 1 submucosal myoma

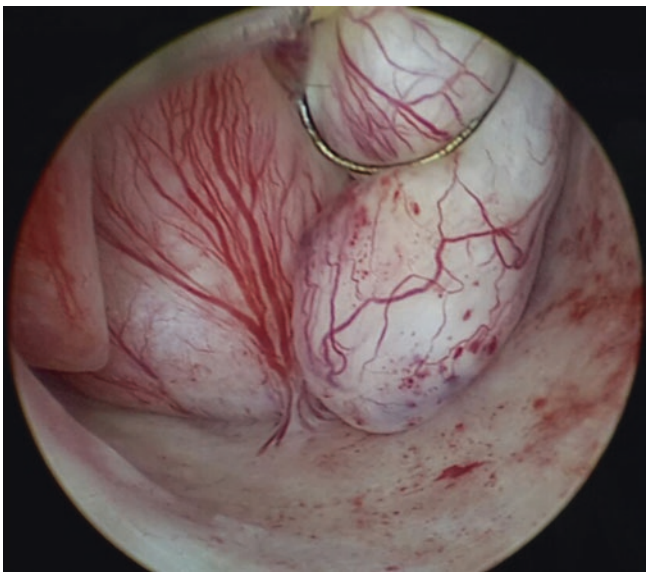


Fig. 3.38 Endometrial polyps with large blood vessels in a background of atrophic endometrium

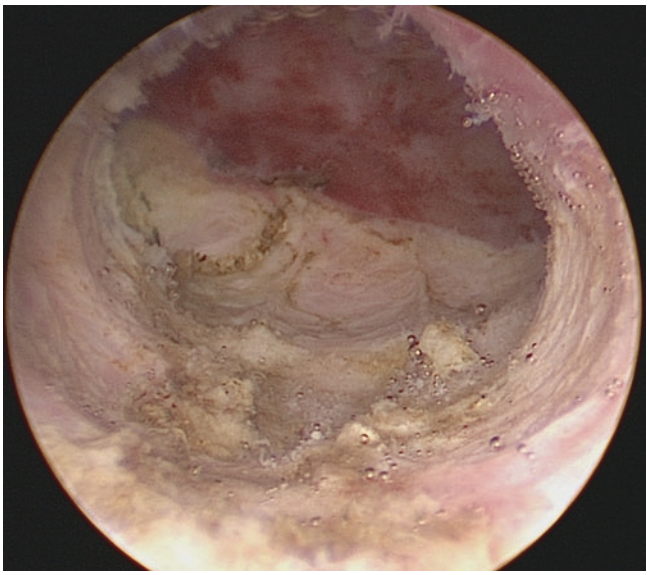


Fig. 3.40 Atrophic uterine cavity, after resection of focal endometrial hyperplasia

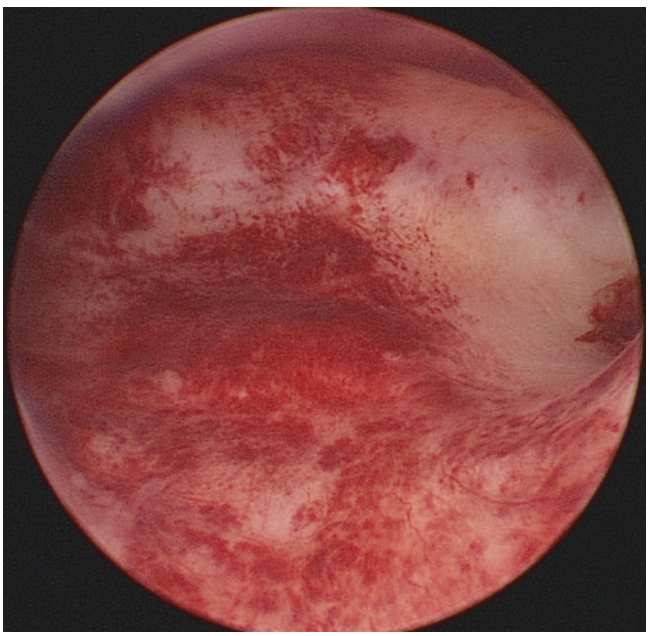


Fig. 3.39 Cystic endometrial hyperplasia associated with tamoxifen in a patient with postmenopausal bleeding

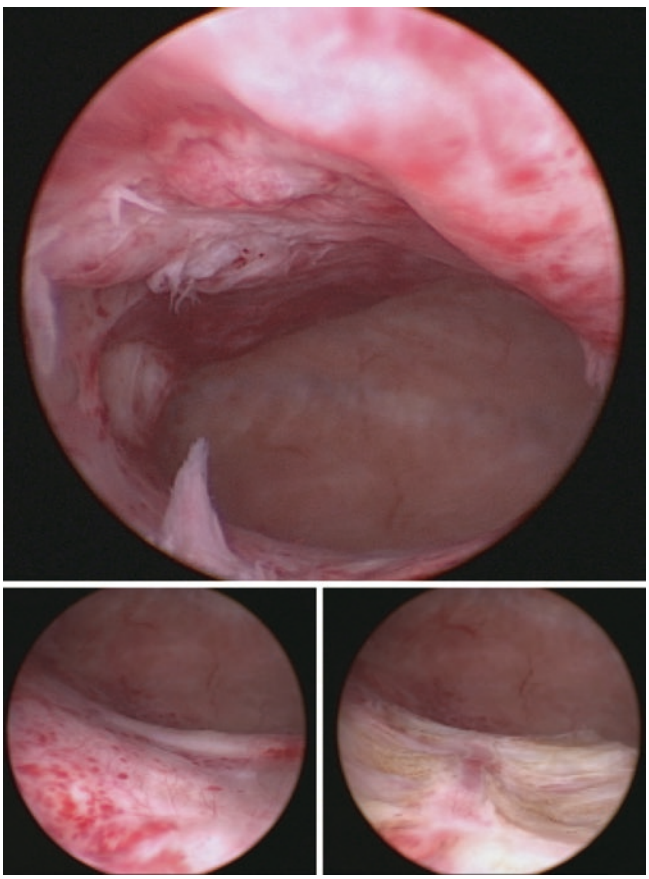


Fig. 3.41 Aromatase inhibitor-modified endometrial lining, with hysteroscopically guided resection

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Part II

The Role of Hysteroscopy in Diagnosis and Management of Cervical Lesions

4

Mykhailo Medvediev

The cervix is the lowermost portion of the uterus and an important organ that provides both transport and protective function. The overall dimensions of the cervix can vary from 2–3 cm to 4–6 cm both in length and in diameter. The cervix, along with the endometrium, undergoes dynamic changes both during the menstrual cycle and during pregnancy, childbirth, and also different age periods of the woman [1–3].

The cervix is divided into few areas. The "portio vaginalis," which contains the ectocervix, projects into the vagina and is visible on speculum placement. In most cases, the "portio vaginalis" is covered by a stratified squamous epithelium that unites with the vaginal squamous epithelium in the fornices. The squamous columnar junction is variable in position depending on age and usually located inside cervical canal in postmenopausal women. In the center of the ectocervix, the external os usually may be visualized [1–3].

The external os continues through the cervix as the endocervix or cervical canal (Fig. 4.1a, b). In the cervical canal, the mucosa has a pleated shape, is represented by multiple bends of connective tissue that resemble glands, and is covered with a single-layered tender cylindrical epithelium (Fig. 4.2). This epithelium produces transparent mucus. Mucus in the cervical canal forms a mucosal plug. Significant cyclic changes occur in endocervical gland secretion relative to estrogen and progestin concentrations. The multilayered squamous epithelium and the cylindrical epithelium meet with each other in the region of the external os and form the junctional zone [1–3].

The internal os is the uppermost region of the cervix prior to entering the endometrial canal. This region is often constricted and is a natural barrier to the hysteroscopist, especially in the nulligravida and the menopausal patient [4–8].

The uterus is composed of multiple elements, of which muscle makes up the greatest percent (up to 70%). The uterine cervix also contains smooth muscle but in much smaller amounts (up to 15%). Interestingly, the smooth muscle content has been shown to decrease as one evaluates cervical tissue segments closest to the endometrial canal (25%), to the middle section (16%), and toward the lower cervical segment (6%) [1].

Most of the cervical stroma is composed of collagen (types I, III, and IV), glycosaminoglycans, and proteoglycans. The glycosaminoglycans dermatan sulfate, chondroitin sulfate, and hyaluronic acid are all found in considerable amounts. In addition, the protein elastin has also been identified [1, 3].

The cervix receives innervation from both parasympathetic and sympathetic neurons. Free nerve endings may reach all layers of the cervix. However, the concentration is lowest in the ectocervix and highest in the endocervix [1, 3].

A gynecologist who owns a hysteroscopy should easily visualize the external cervical canal and pass through the canal into the uterine cavity, taking into account the features of the 30° optics. In some cases, this is a complicated stage of hysteroscopy and can lead to a false rout formation (Fig. 4.3) [1, 3, 7–9].

Visualization of the cervical canal is an integral part of modern hysteroscopy. When examining this zone, the hysteroscopist may encounter a variety of pathological changes, such as cervical pregnancy, cervical leiomyoma, endometrial polyp and cervical canal, fistula, perforation and false stroke, pancreatic cysts, IUD mustache, cervical cancer and endometrium, and many other pathologies [1–9].

Selected hysteroscopic images of the common pathology of the cervical canal are presented in this chapter (Figs. 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, 4.12, 4.13, 4.14, 4.15, 4.16, 4.17, 4.18, 4.19, and 4.20).

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_4

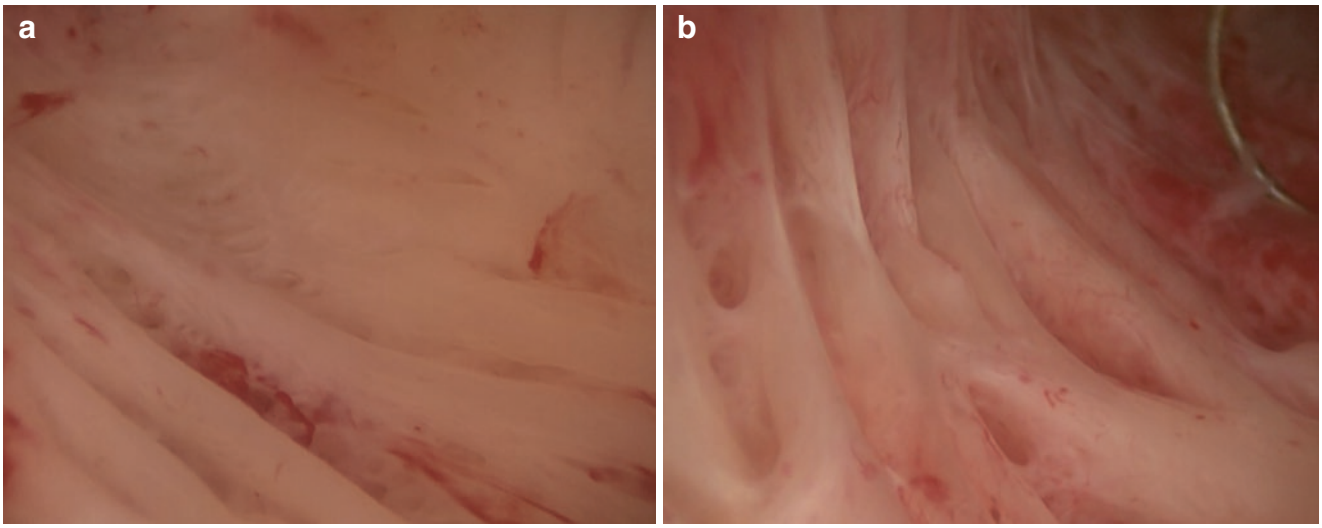

Fig. 4.1 (**a**) Normal view. Folding of cervical canal. (**b**) Normal view. Folding of cervical canal during resectoscopy

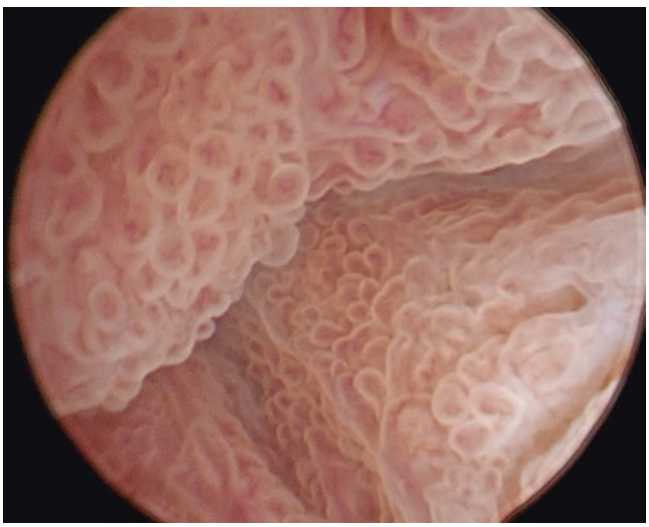

Fig. 4.2 Cylindrical epithelium cervical canal through vaginoscopic approach

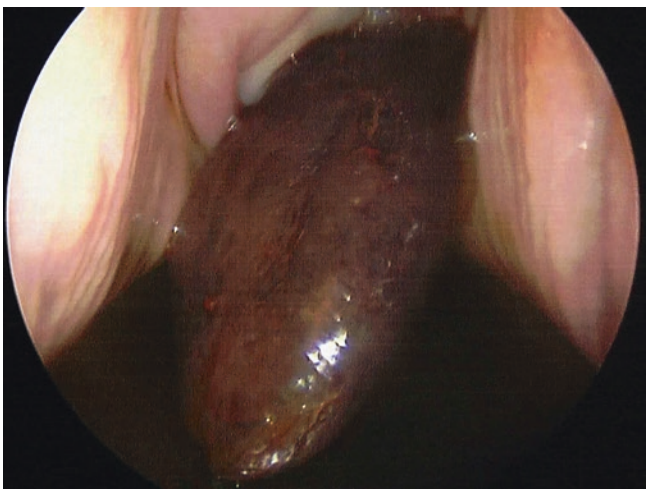

Fig. 4.4 Endometrial polyp showing in the vagina (courtesy of Sunita Taldudwadkar)

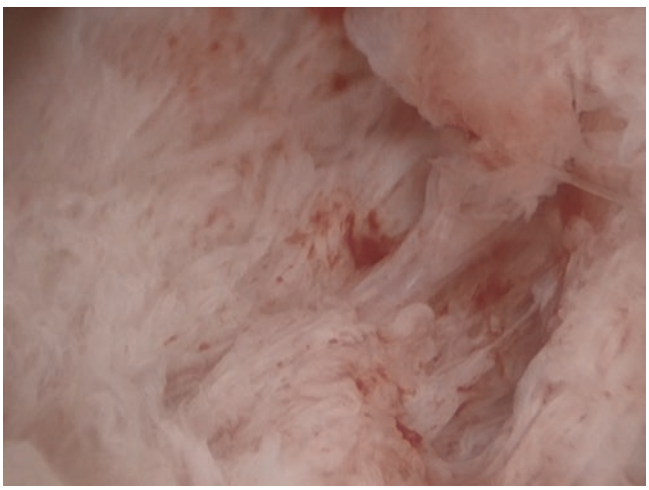

Fig. 4.3 False rout after blind dilation

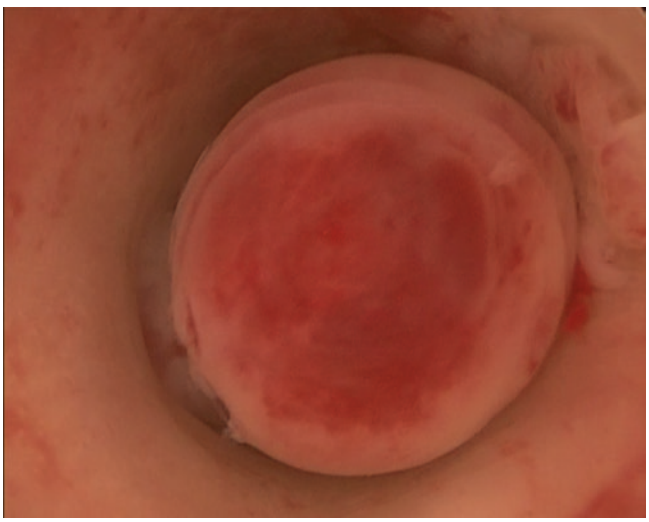

Fig. 4.5 Endometrial polyp showing in the endocervical canal

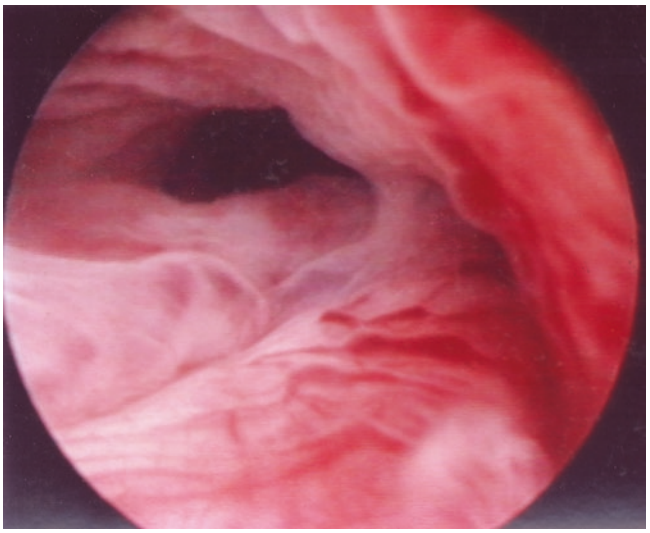

Fig. 4.6 Cervical myoma arising from the upper canal (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

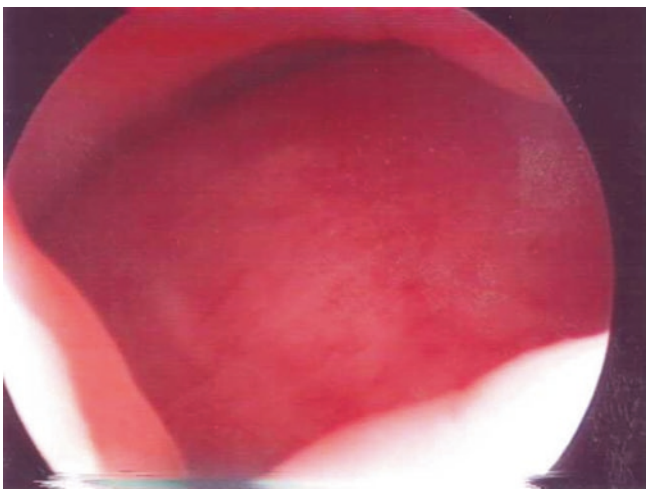

Fig. 4.7 Myoma showing through the external cervical os through vaginoscopy (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

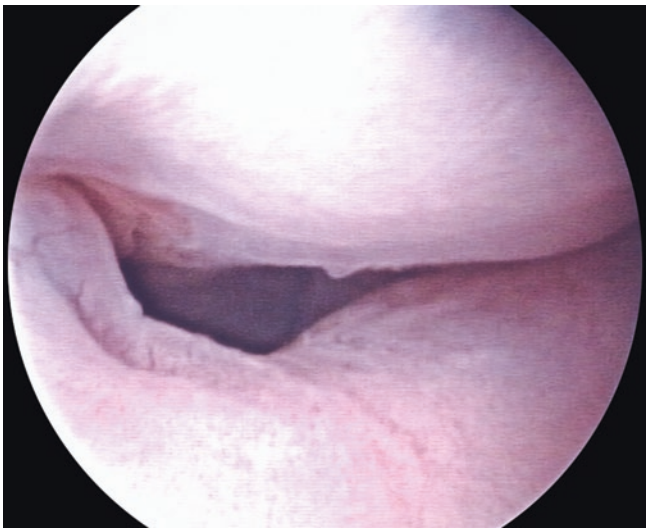

Fig. 4.8 Cervical incompetence through hysteroscopy (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

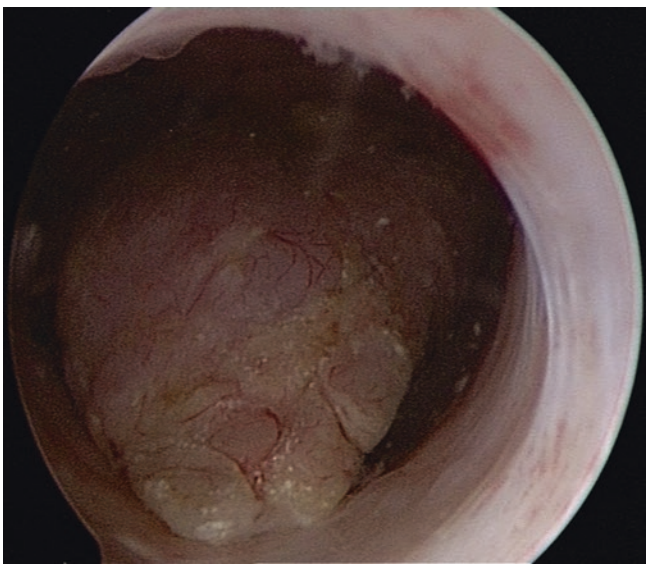

Fig. 4.9 Endometrial cancer involving the upper part of the endocervix (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

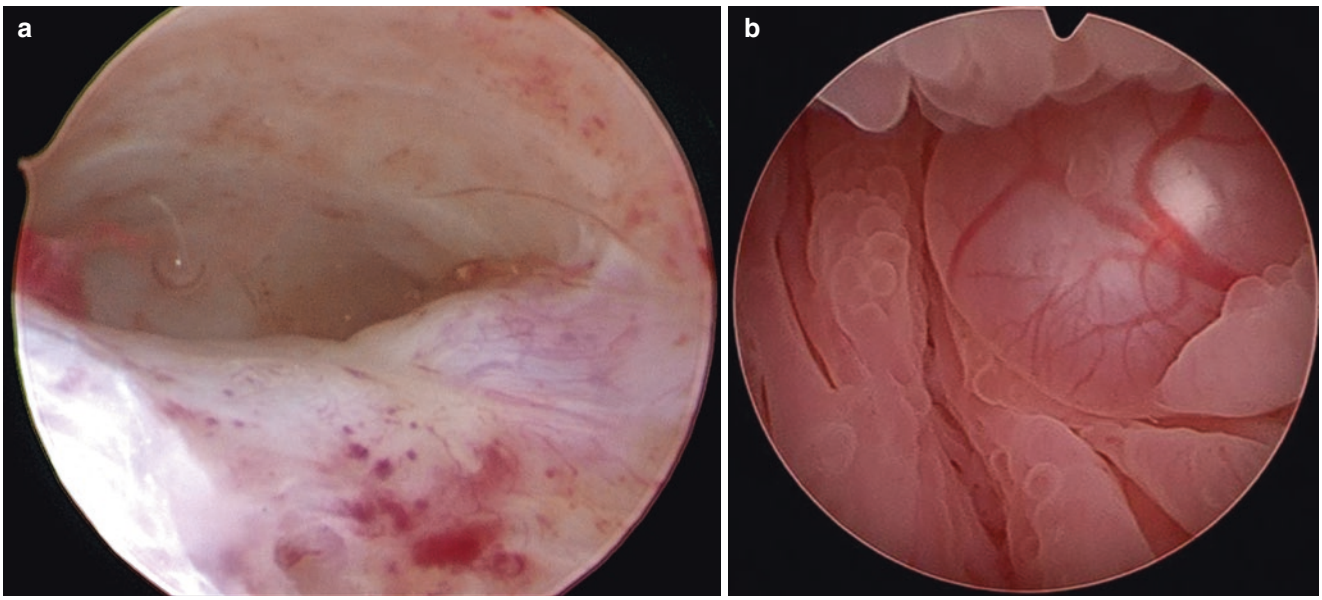

Fig. 4.10 (**a**) Nabothian cyst protruding to posterior isthmical wall. (**b**) Nabothian cyst (courtesy of Luis Alonso)

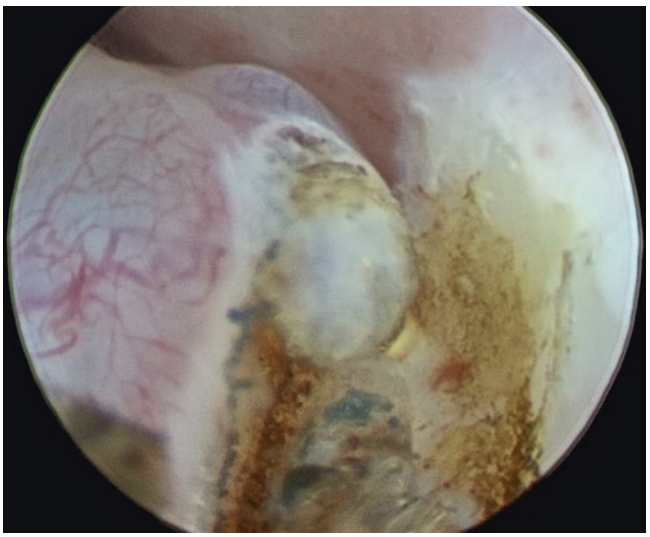

Fig. 4.11 Nabothian cyst laser removal

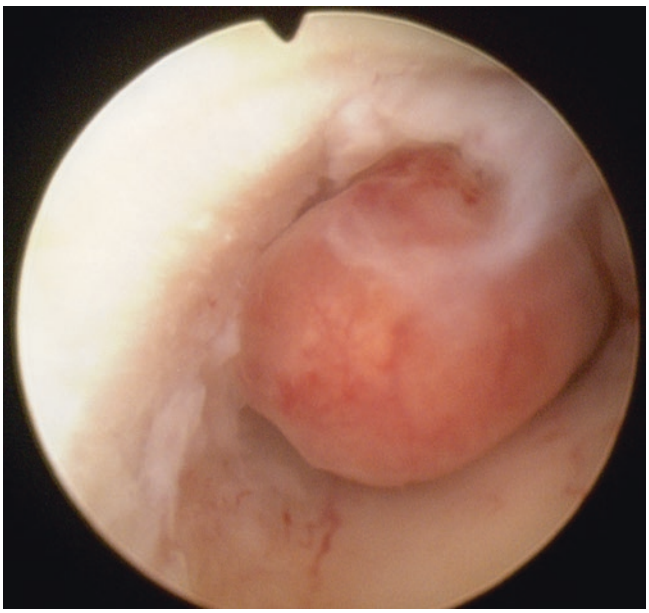

Fig. 4.12 Cervical polyp (courtesy of Jude Okohue)

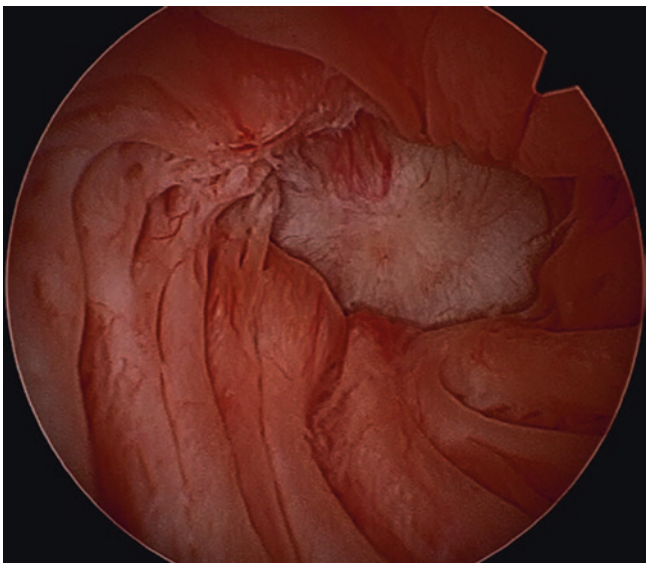

Fig. 4.13 Cervical stump (courtesy of Luis Alonso)

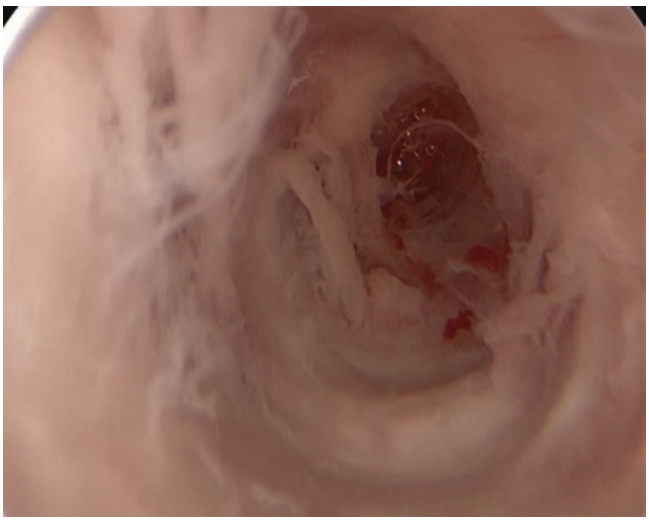

Fig. 4.15 Isthmical synechia in patient with HUB

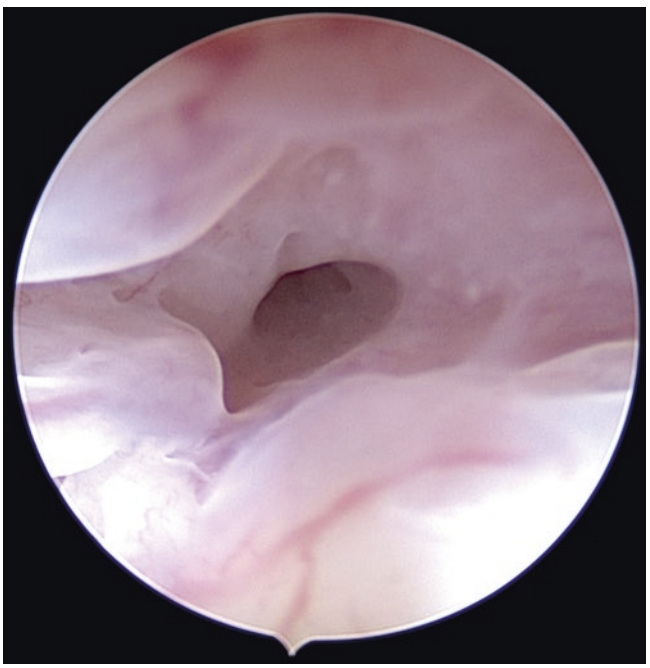

Fig. 4.14 Internal os stenosis (courtesy of Haresh Vaghasia)

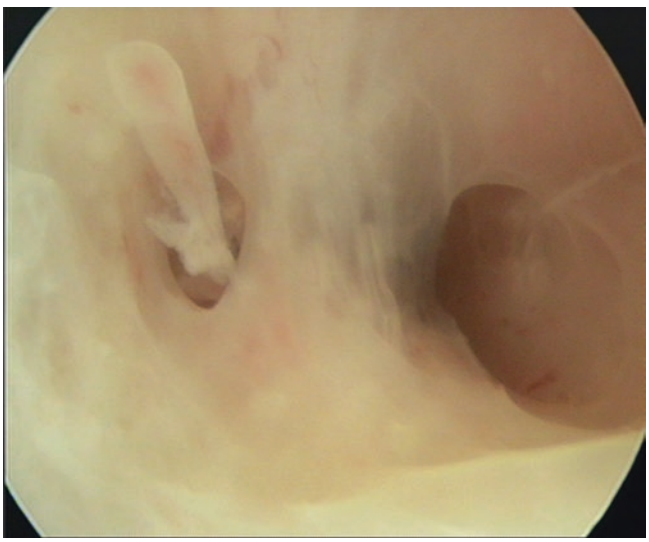

Fig. 4.16 Isthmico-cervical adhesion (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

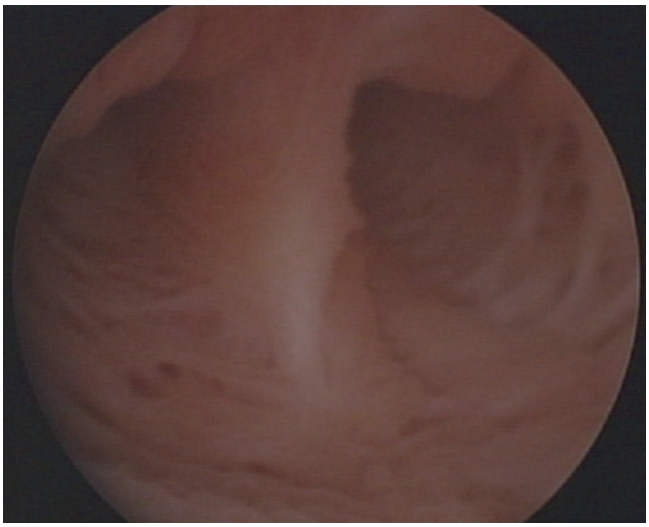

Fig. 4.17 Endocervical septum (courtesy of Alicia Ubeda Hernandez, Barcelona, Spain)

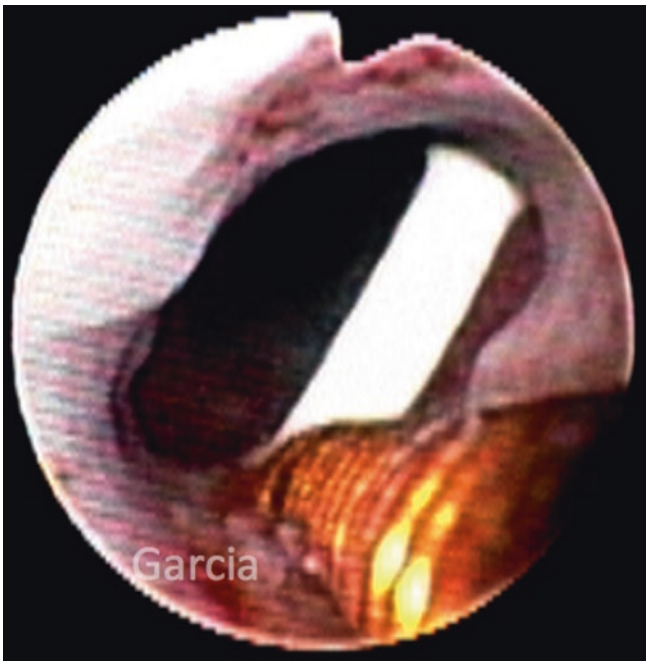

Fig. 4.19 Copper IUD embedded in cervix (courtesy of Amy Garcia, New Mexico, USA)

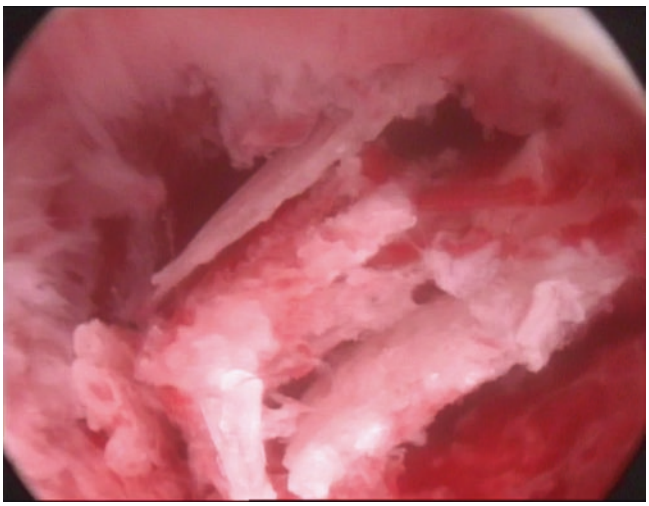

Fig. 4.18 Cervical canal osseous metaplasia 7 years after 17-week abortion

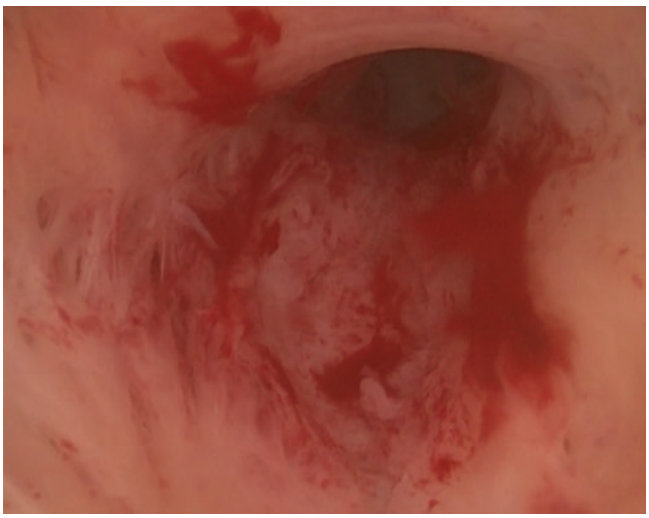

Fig. 4.20 Cervical canal distorted by blunt Hegar's dilator use before resectoscopy

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Uterine Polyps

5

José Metello and João Mairos

5.1 Uterine Polyps

Uterine polyps refer to focal hyperplastic growths protruding from the uterine inner lining covered by epithelium [1]. They are most often benign. They can be categorized according to their location (endometrial, cervical, or vaginal), presence of a stalk (pedunculated—usually narrow and elongated versus sessile), and histological type [2].

5.2 Epidemiology

It is difficult to estimate the true incidence of polyps. With the widespread of high-resolution ultrasound devices endometrial polyps have become one of the most common endometrial abnormalities reported.

According to several authors the prevalence of endometrial polyps varies between 7.8% and 50% [3–6]. While it will be lower in a young asymptomatic population, below 10% [7], it has been reported to be around 15.3% in infertile patients [8] and over 25% in patients presenting with abnormal uterine bleeding.

The malignant potential of endometrial polyps is unknown. The reported incidence of carcinoma confined to endometrial polyps varying between 0% and 4.8%, depending on the selection of patients and the methods used in making the diagnosis [9, 10].

The pathogenesis remains ambiguous. It seems that several factors are involved, including diabetes mellitus, obesity, hypertension, age, menopause status, and steroid hormone receptors [11, 12].

Many genetic alterations seem to be related to the polyp etiology. Dal Cin et al. categorized in 1995 [13] several cytogenetic changes among polyps involving chromosomes 6, 7, and 12. Other investigations reported on the involvement of bcl-2 and bax genes.

Some authors report on the role of estrogen and progesterone receptors, which might be unbalanced in this condition [14–17]. There can be an overexpression of estrogen receptors during the proliferative phase not properly balanced by progesterone receptors [16]. This can help to explain why cases related to higher exposition to estrogen like heavier weight, late menopause, and unopposed estrogen use (as in hormone replacement therapy or polycystic ovary syndrome) [18–22] are positively correlated with the presence of polyps.

From the histological viewpoint, several classifications have been proposed. Di Spiezio proposed [23]:

- *Hyperplastic polyps:* Arising from the basal endometrial layer, which is sensitive to estrogen, they are the result of the estrogen stimulation not balanced by the effect of progestin. They can be associated with diffuse endometrial hyperplasia (EH).
- *Atrophic polyps:* Typical of postmenopausal age, they are generally regressive alterations of functional or hyperplastic polyps.
- *Functional polyps:* They show glandular alterations similar to those of the surrounding endometrium, as they respond to the hormonal stimuli of the menstrual cycle.
- *Adenomyomatous polyps:* They are characterized by varying amounts of smooth muscle cells and fibrous tissue. The "atypical" forms are characterized by the concomitant presence of benign endometrial glands and stroma with structural atypia consisting mainly of smooth muscle, and in which the likelihood of association with endometrial cancer transformation is about 9%.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_5) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_5

– *Pseudopolyps:* Small sessile lesions whose structure is identical to the surrounding endometrium; they are detected only in the secretory phase of the menstrual cycle, and then disappear with the menstrual flow.

Cervical polyps are less common and have been described in 2–5% of cases [24]. They can be found most commonly in the endocervical canal as demarcated by the transformation zone. Although they arise from glandular hyperplasia their etiology is not clear. They are commonly pedunculated, most often benign, in over 95% of the cases. Often they have a fibrovascular core of stroma surrounded by a papillary proliferation of squamous or glandular epithelium [24].

The etiology is unknown, but differently than endometrial polyps it is believed to be related to inflammation.

Vaginal polyps are not commonly reported and they have been described as tubulo-squamous [25] (Figs. 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 5.10, 5.11, 5.12, 5.13, 5.14, 5.15, 5.16, 5.17, 5.18, 5.19, 5.20, 5.21, 5.22, 5.23, 5.24, 5.25, 5.26, 5.27, 5.28, 5.29, 5.30, 5.31, 5.32, 5.33, 5.34, 5.35, 5.36, 5.37, 5.38, 5.39, 5.40, 5.41, 5.42, 5.43, 5.44, 5.45, 5.46, 5.47, 5.48, 5.49, 5.50).

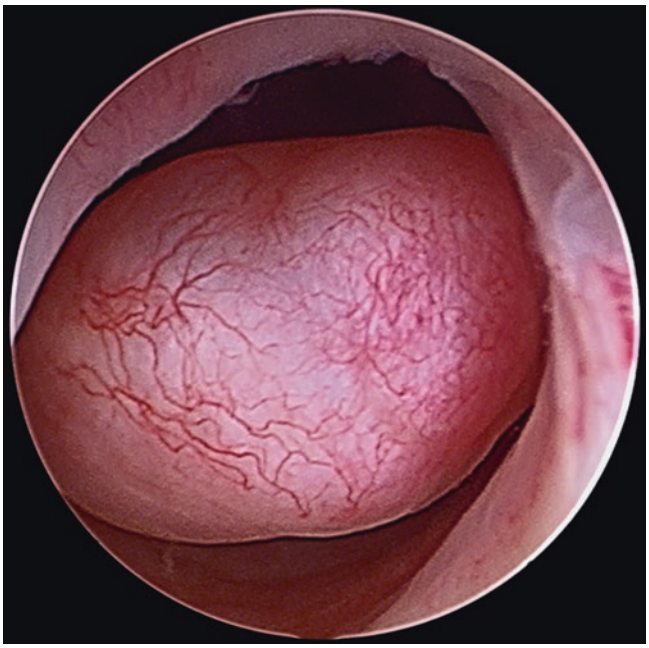

Fig. 5.2 Polyp

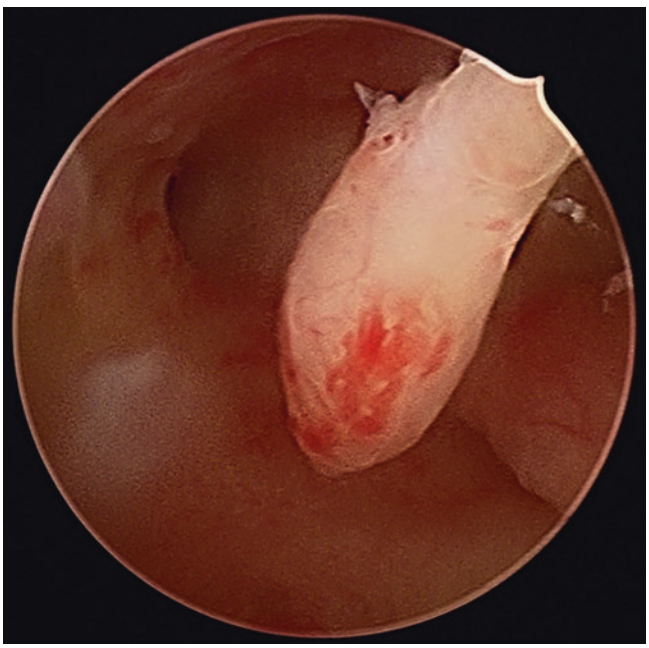

Fig. 5.1 Polyp

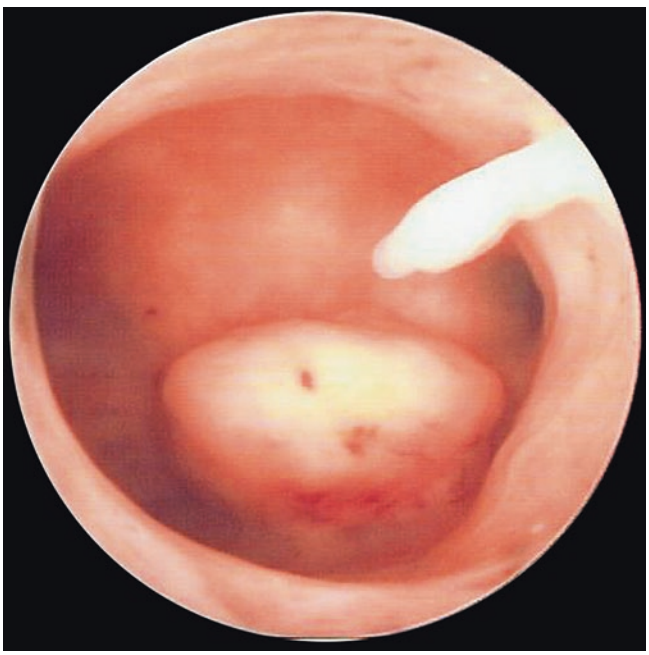

Fig. 5.3 Polyps

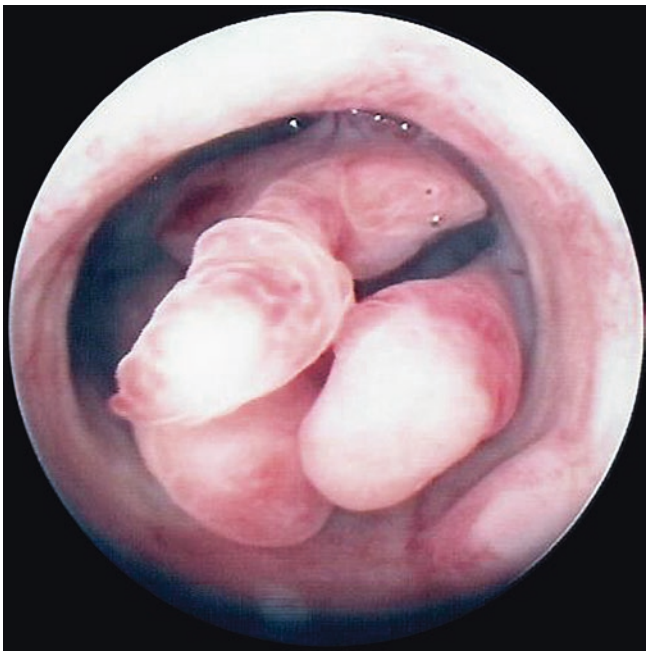

Fig. 5.4 Polyps

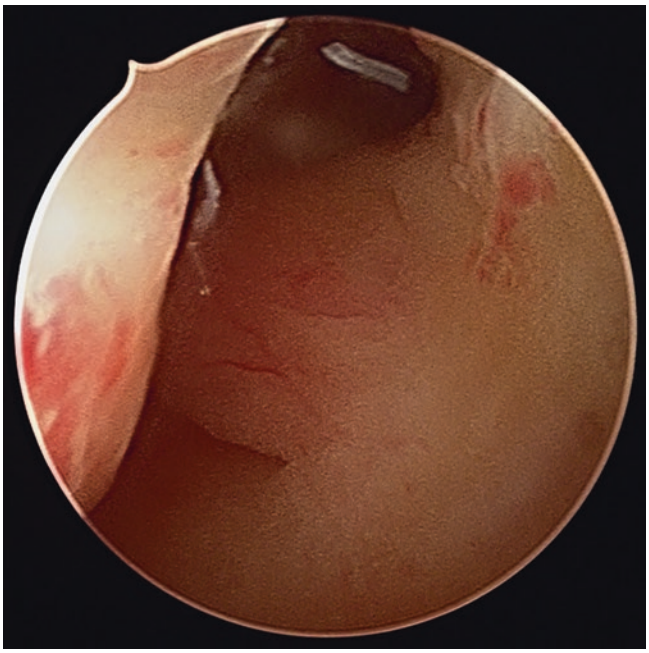

Fig. 5.6 Polyp

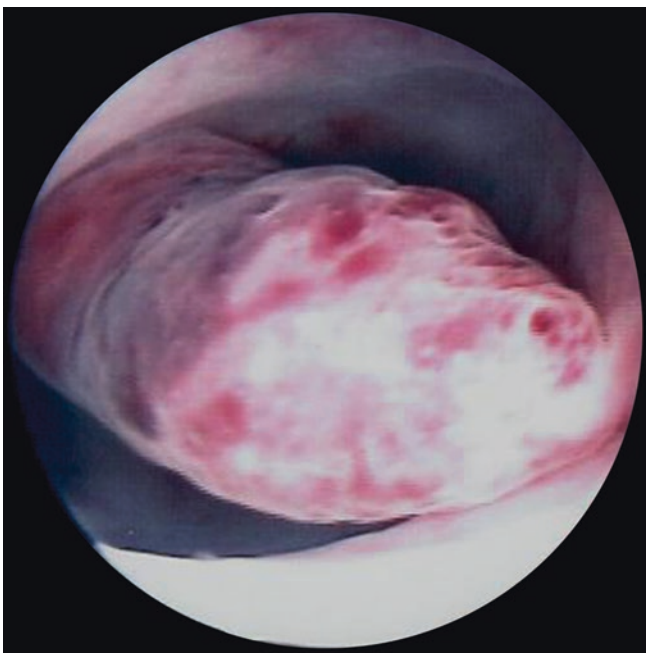

Fig. 5.5 Polyp

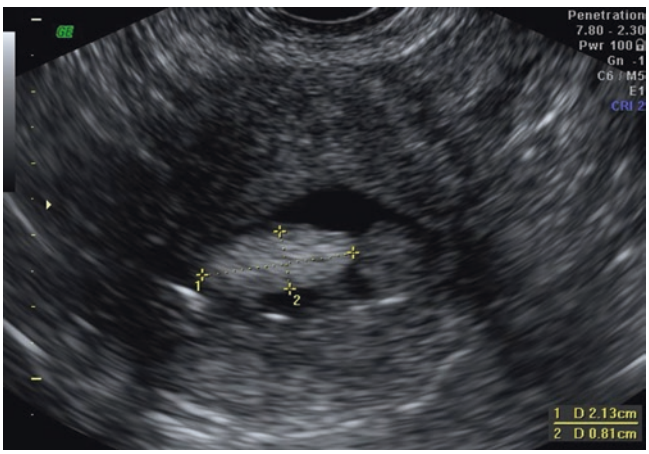

Fig. 5.7 Hysterosonography polyp

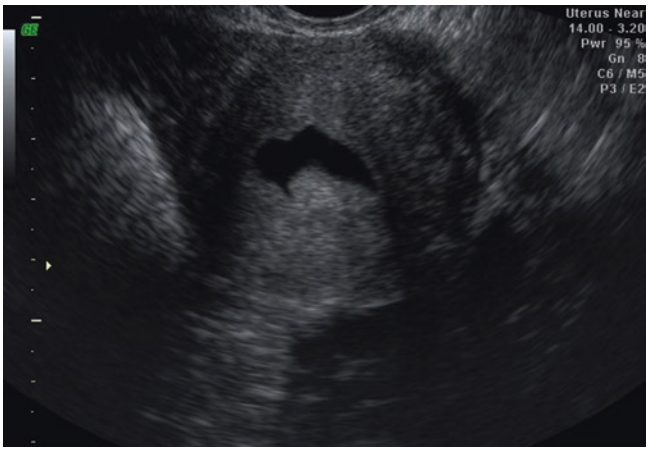

Fig. 5.8 Hysterosonography polyp

Fig. 5.9 Hysterosonography polyp

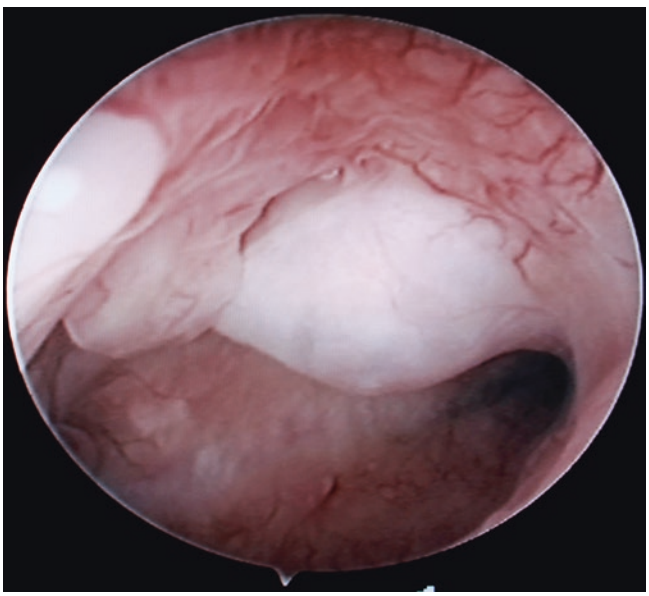

Fig. 5.10 Sessile polyp

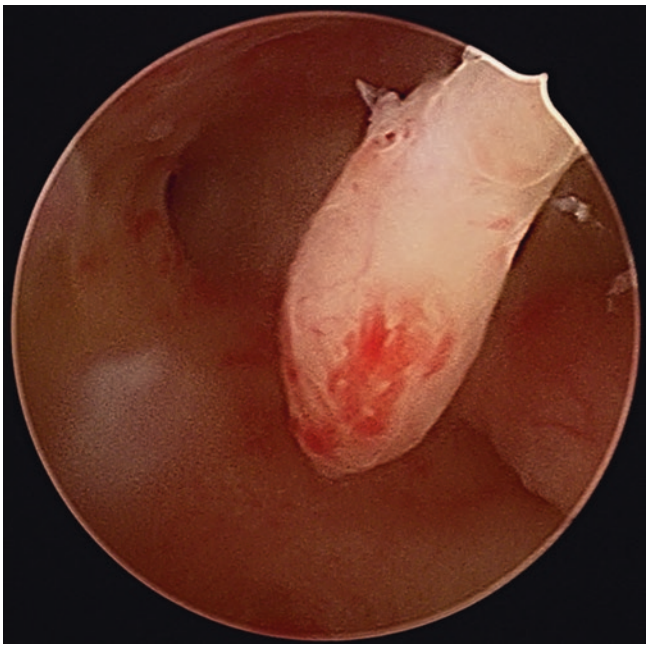

Fig. 5.11 Polyp

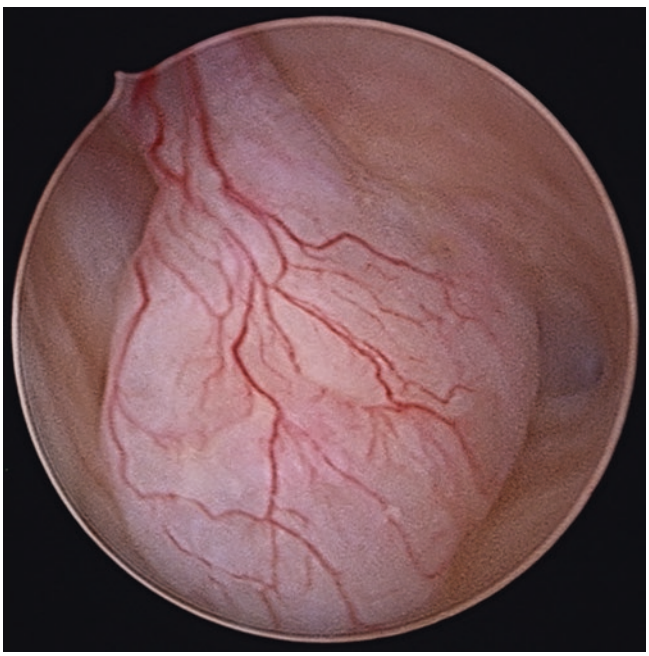

Fig. 5.12 Polyp

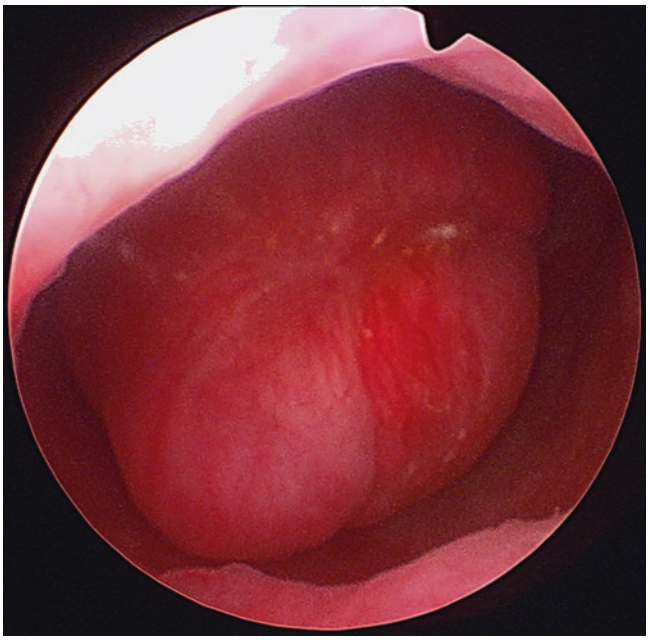

Fig. 5.13 Polyp

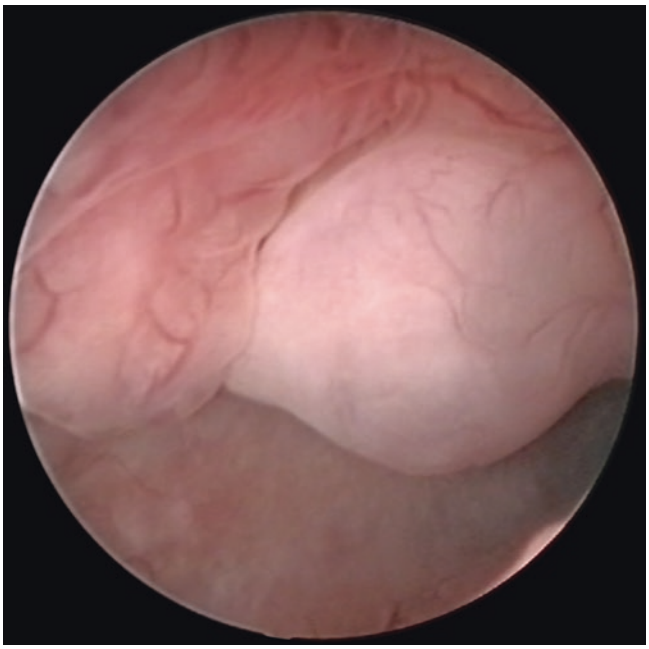

Fig. 5.15 Sessile polyp

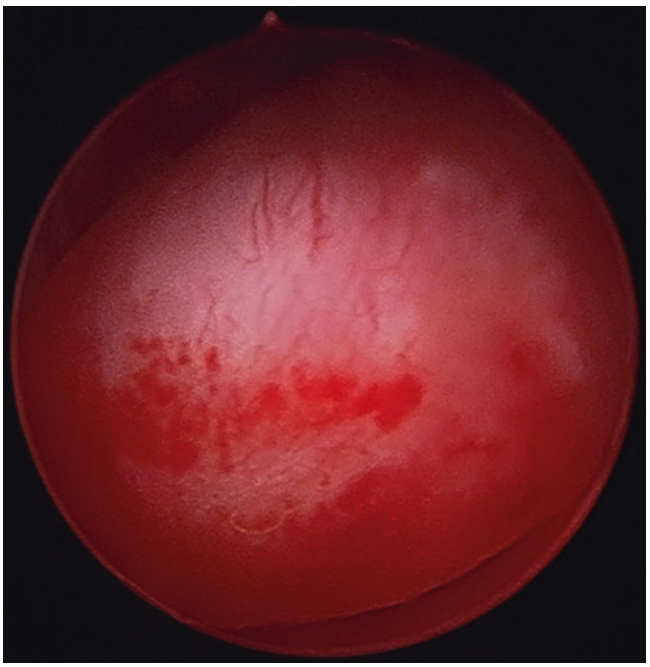

Fig. 5.14 Polyp

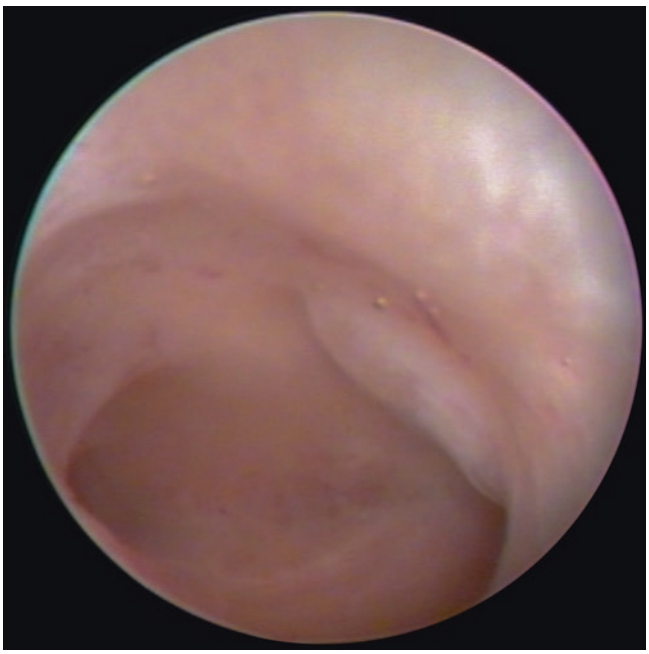

Fig. 5.16 Sessile polyp

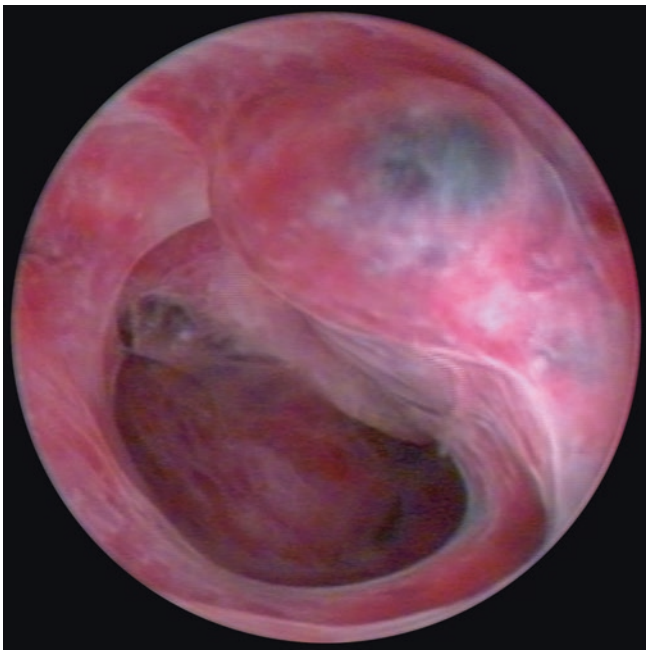

Fig. 5.17 Sessile polyp

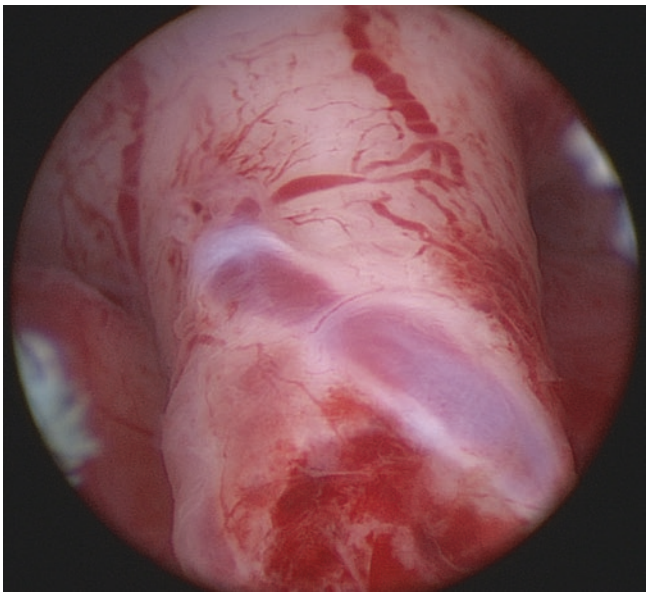

Fig. 5.19 Polyp—courtesy of Dr. Alejandro Gonzalez

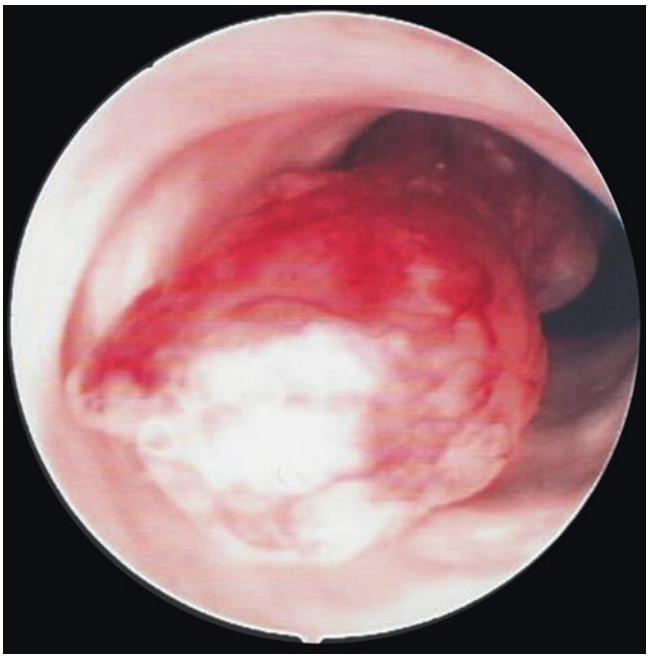

Fig. 5.18 Polypectomy of polyp with carcinoma at the base—office hysteroscopy

Fig. 5.20 Polyp–courtesy of Dr. Sushma Deshmukh

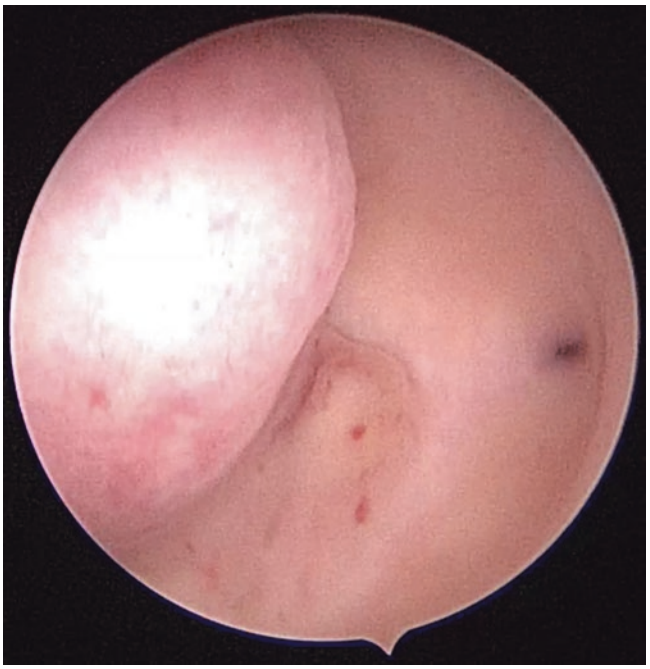

Fig. 5.21 Polyp–courtesy of Dr. Sushma Deshmukh

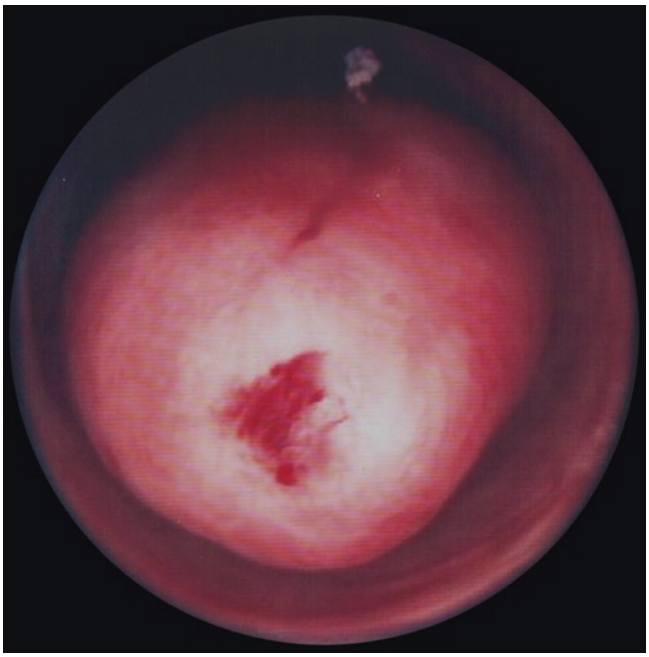

Fig. 5.23 Polyp

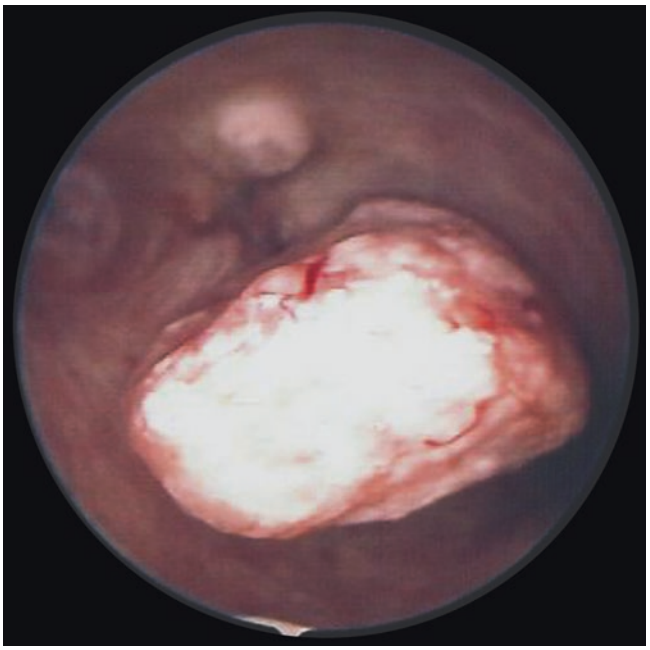

Fig. 5.22 Polyp

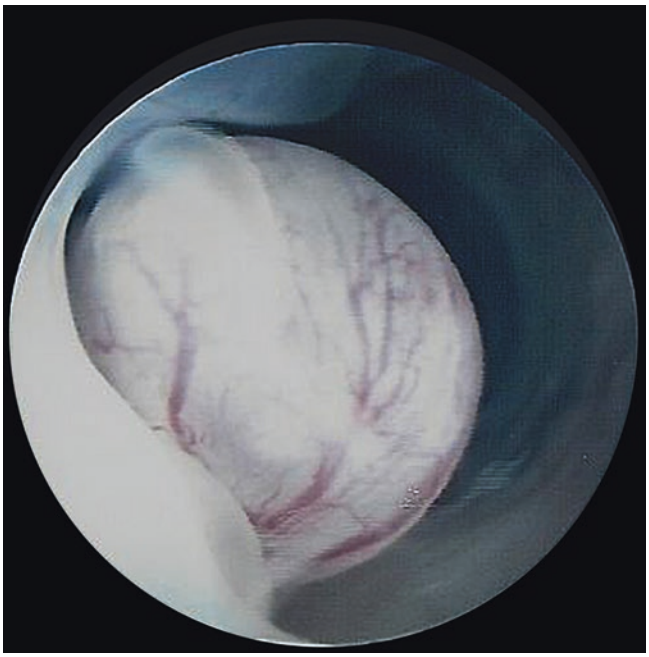

Fig. 5.24 Polyp

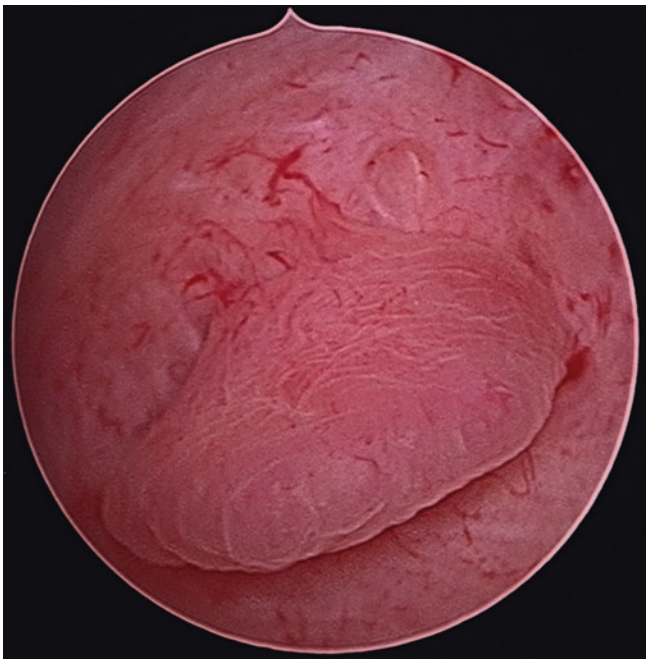

Fig. 5.25 Polyp

Fig. 5.27 Polyp

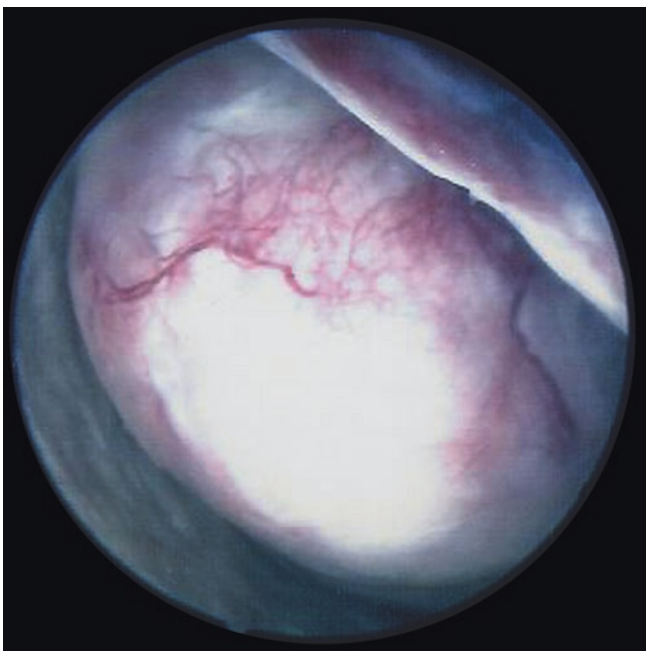

Fig. 5.26 Polyp

Fig. 5.28 Gigantic polyp

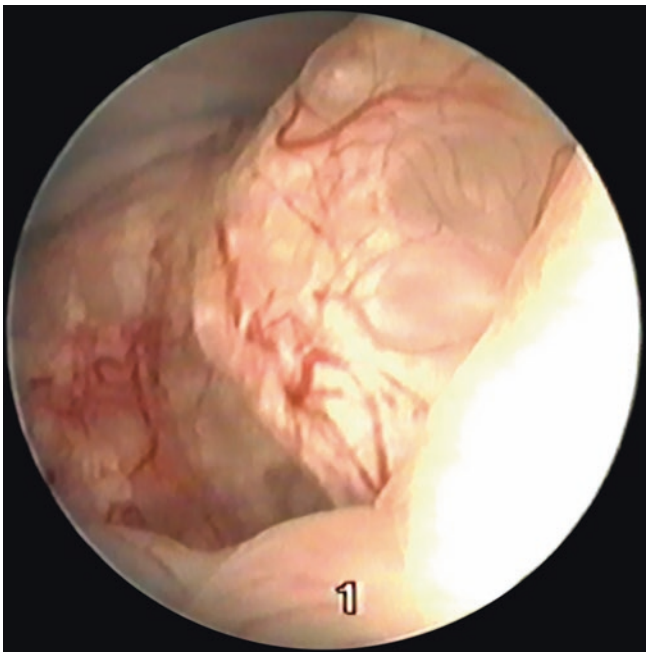

Fig. 5.29 Gigantic polyp

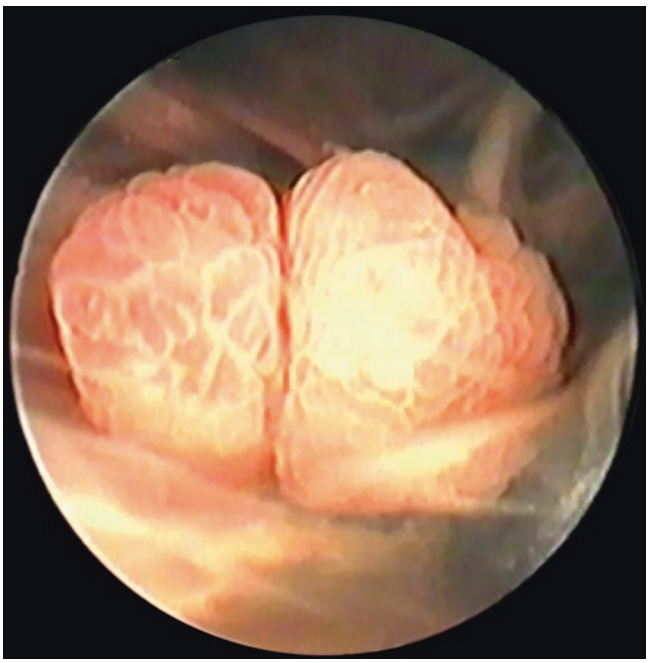

Fig. 5.31 Endocervical polyp

Fig. 5.30 Polyp

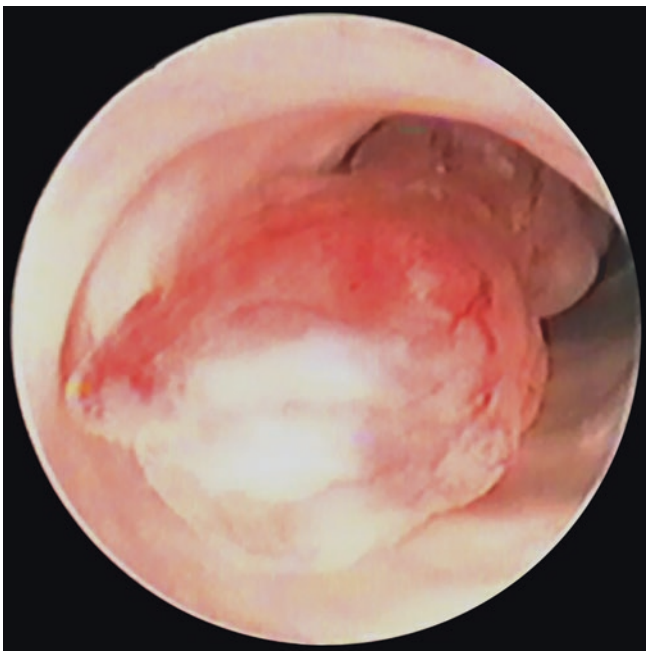

Fig. 5.32 Polyp

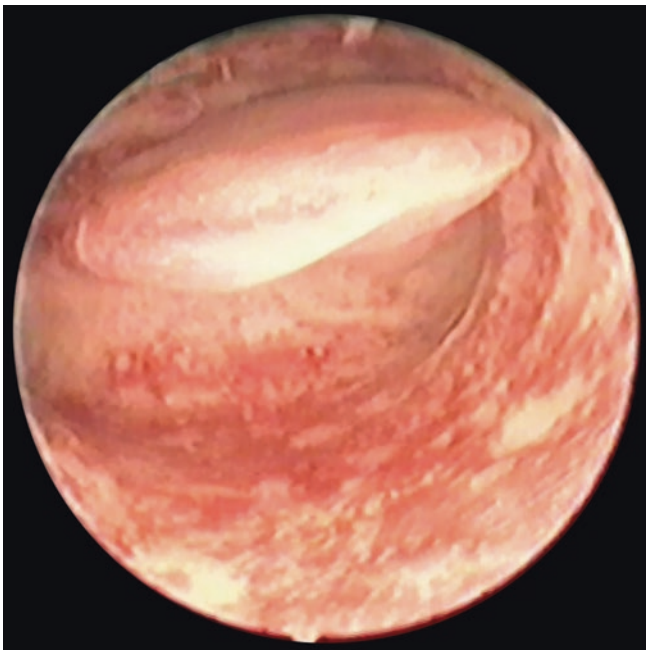

Fig. 5.33 Small fundal polyp

Fig. 5.35 Polyp

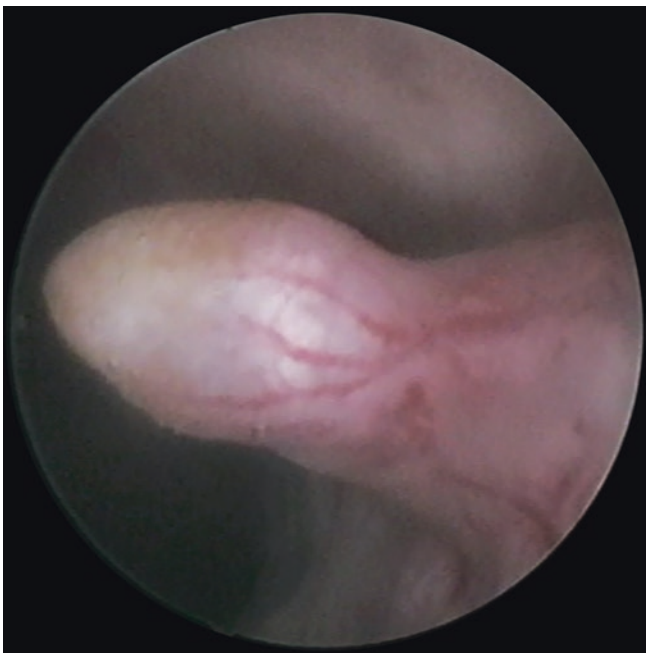

Fig. 5.34 Polyp

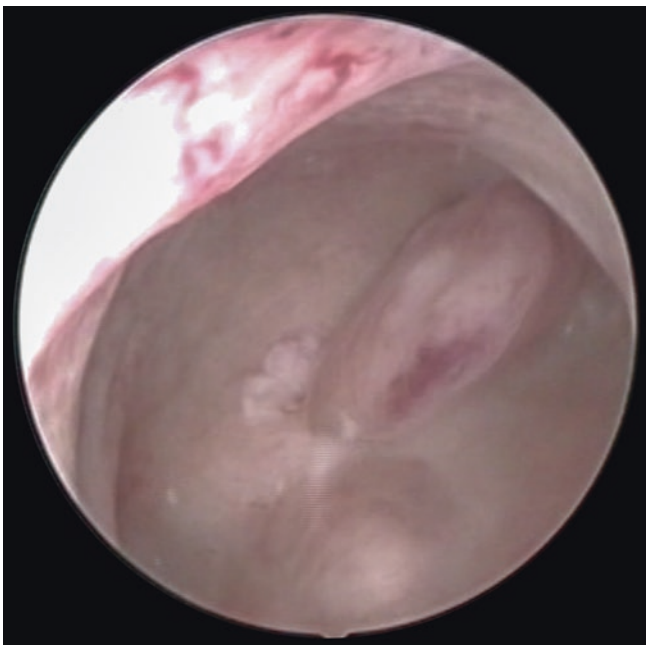

Fig. 5.36 Polyp and sub-mucous myoma indentation

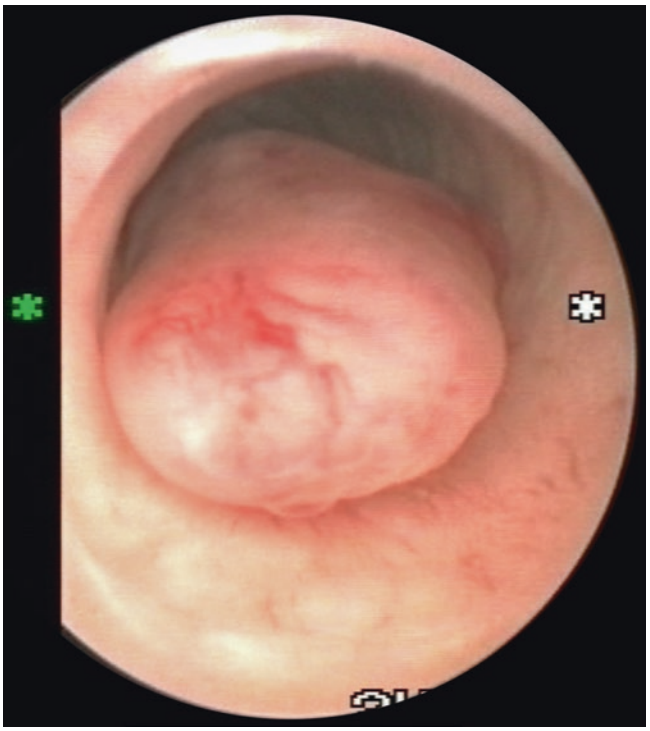

Fig. 5.37 Polyp

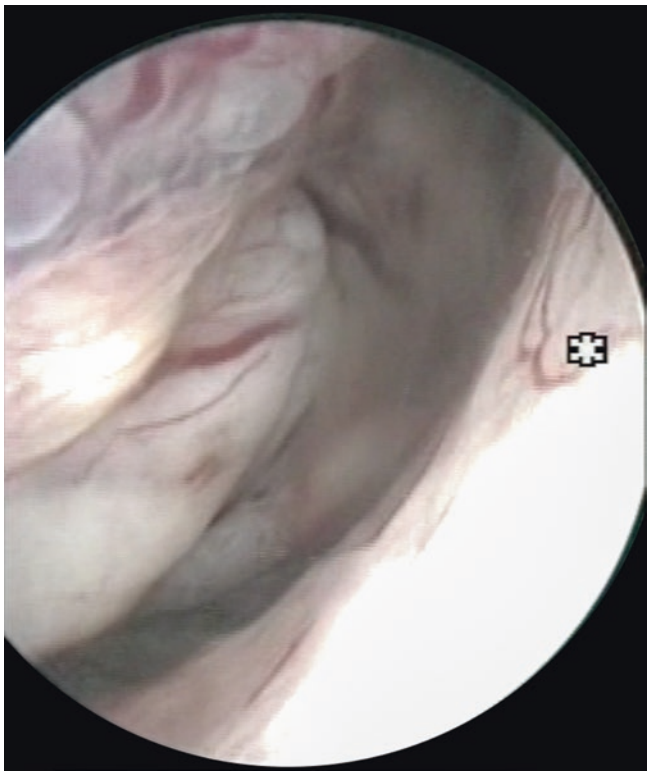

Fig. 5.39 Polypoid carcinoma

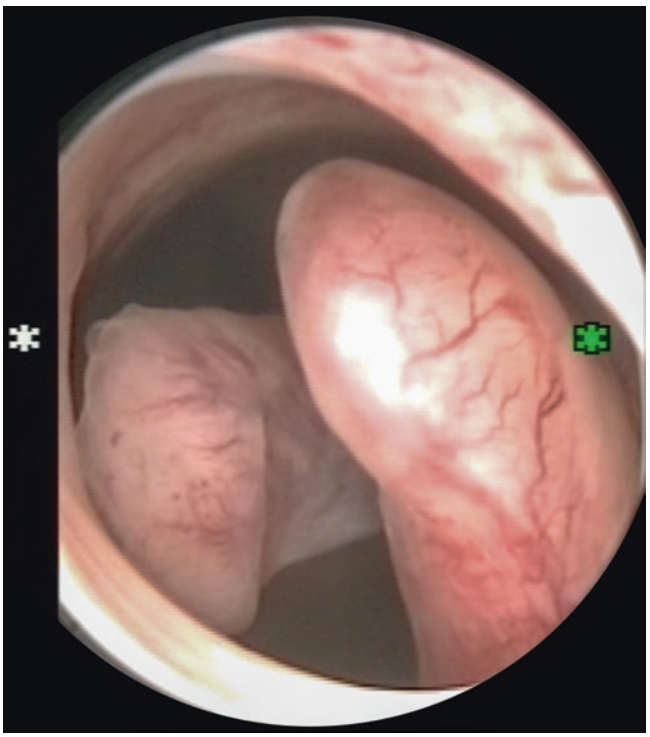

Fig. 5.38 Two polyps

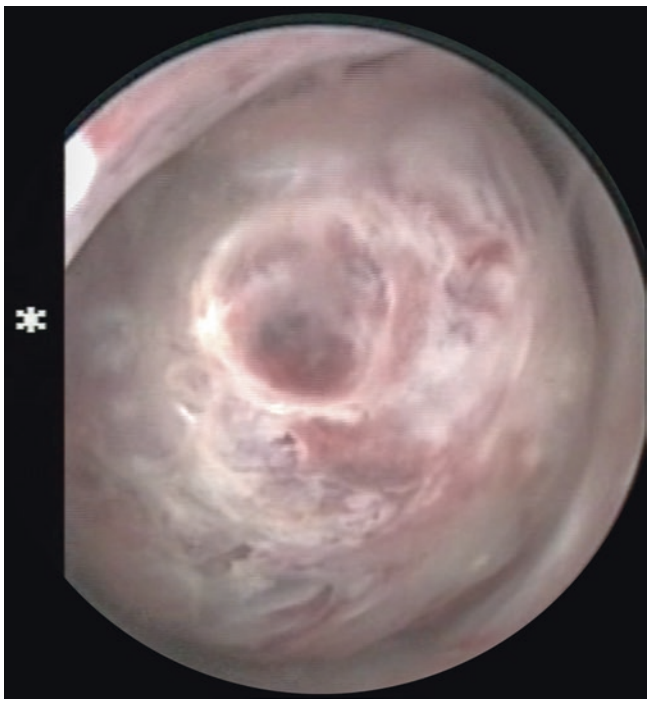

Fig. 5.40 Polypoid carcinoma

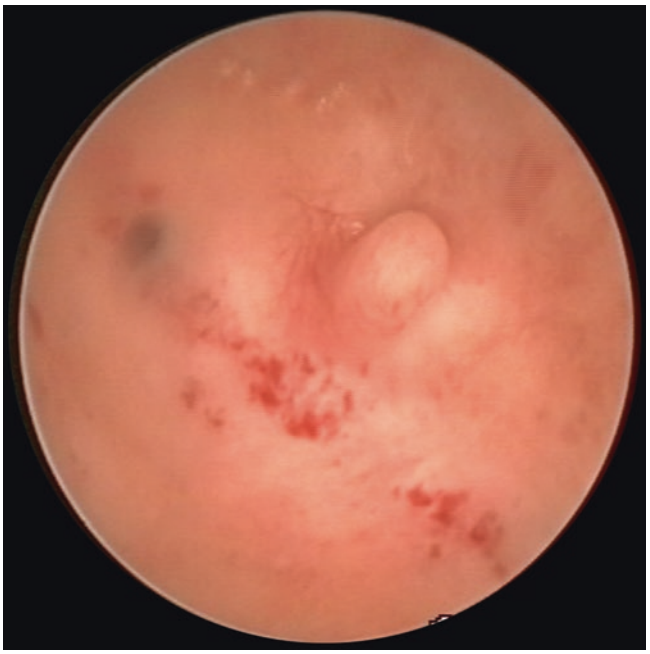

Fig. 5.41 Small fundal polyp

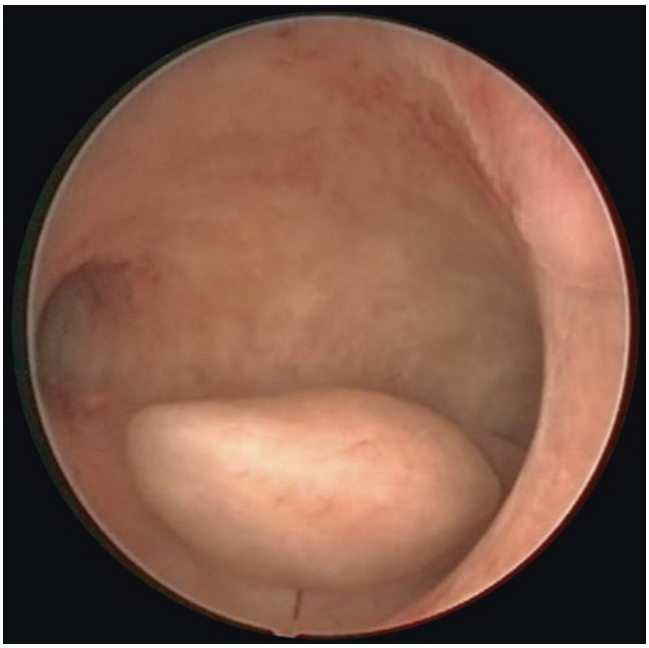

Fig. 5.43 Polyp

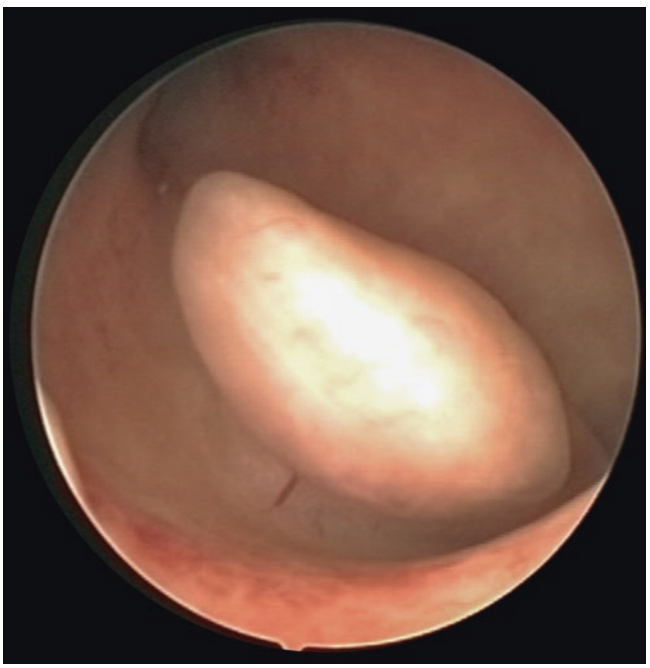

Fig. 5.42 Polyp

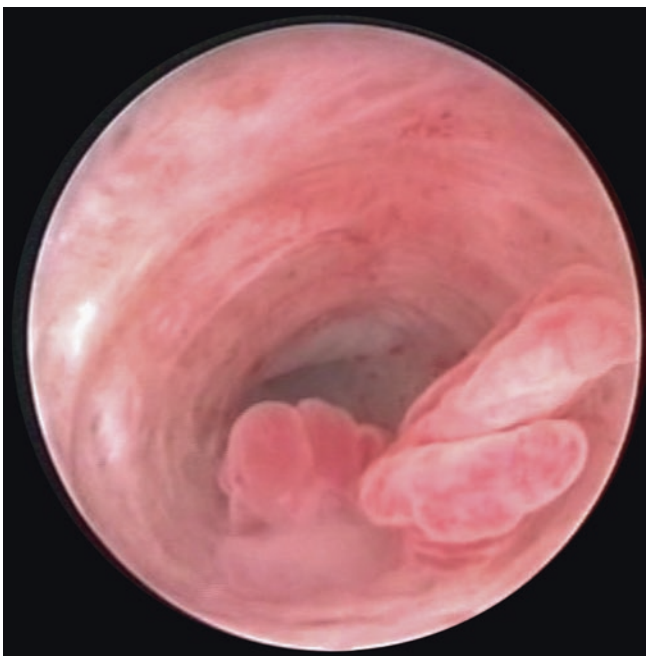

Fig. 5.44 Cervical polyps

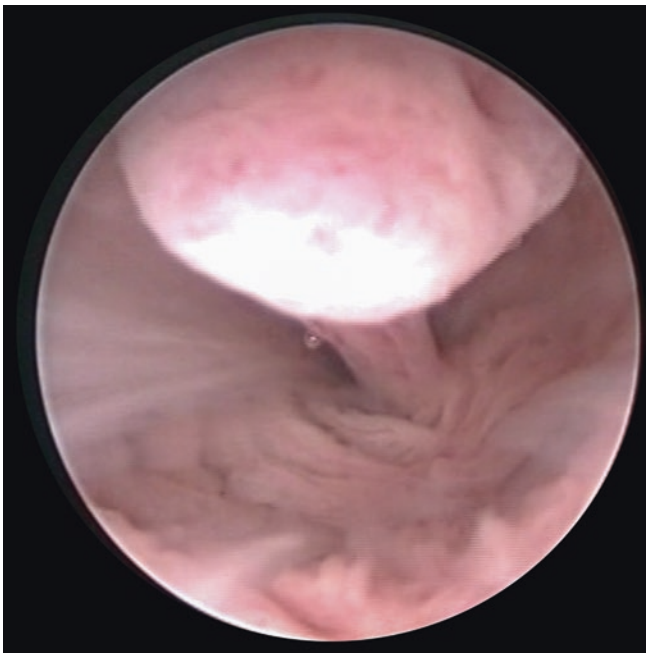

Fig. 5.45 Cervical polyps

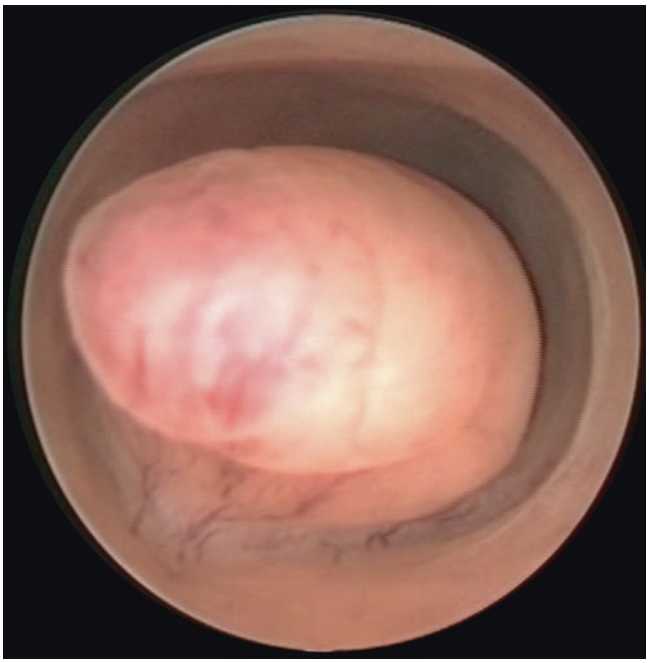

Fig. 5.47 Polyp

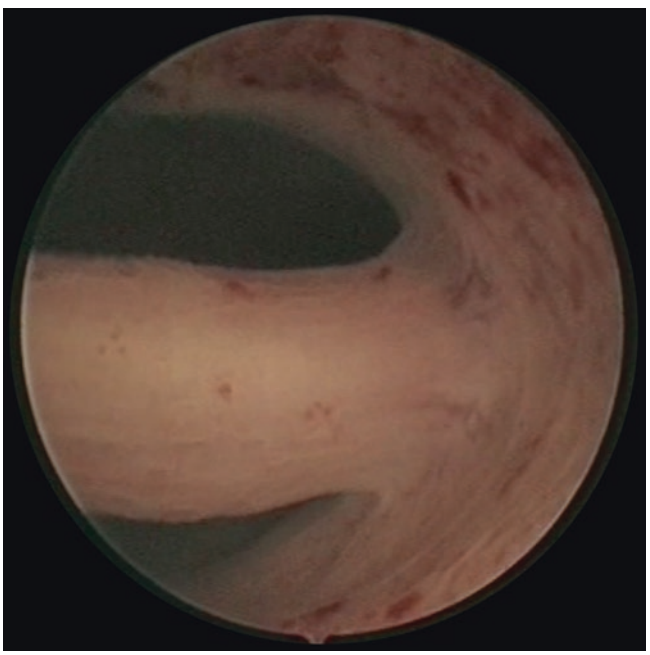

Fig. 5.46 Polyp

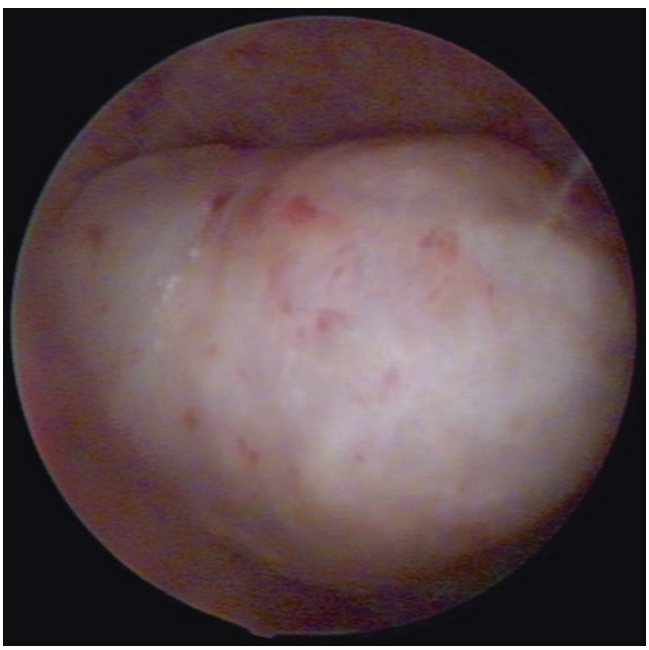

Fig. 5.48 Polyp

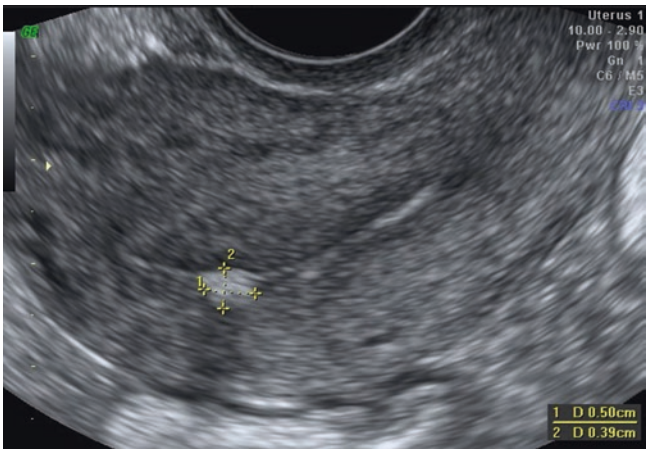

Fig. 5.49 Ultrasound with hyperechogenic polyp

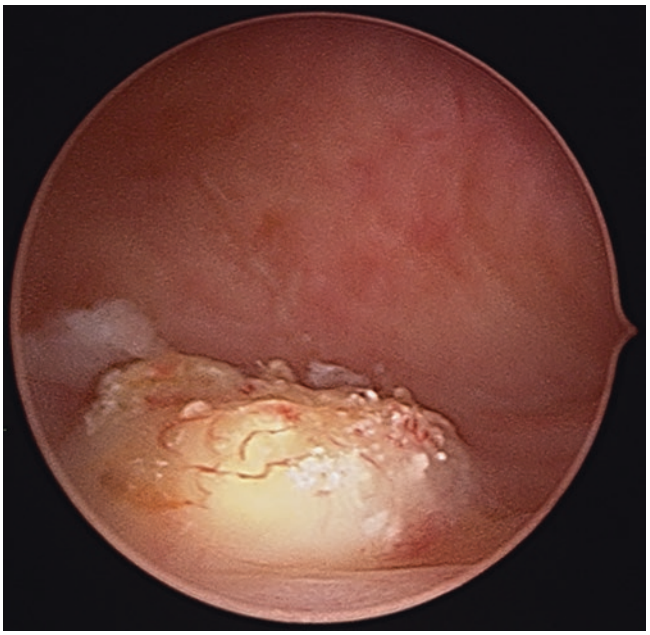

Fig. 5.50 Sessile polyp—4 months postpartum placental remnants

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Hysteroscopy and Fibroids

6

Ricardo Bassil Lasmar, Ivano Mazzon,
and Bernardo Portugal Lasmar

6.1 Introduction

Uterine fibroid is a benign neoplasm originating from smooth muscle cells of the myometrium whose development depends on the interaction between steroid hormones, growth factors, cytokines, and somatic mutations. Uterine fibroids are monoclonal tumors, with no known triggering factor, which demonstrates the need to elucidate this disease.

All myomas are born from myometrial cells. The myocytes are initially intramural; that is, they have all their content in the myometrium and can be located anywhere in the uterus, being classified according to this location in intramural, submucosal, and subserosal.

Its prevalence is 70–80% in women aged 50 years, according to sonographic and histological studies. A study assessing uteri submitted to post-hysterectomy in perimenopausal women showed myoma in 77% of the cases [1].

Most of the time fibroids are diagnosed adventitiously on routine exams and are clinically insignificant; however, leiomyomas may have high morbidity due to menstrual disorders (such as increased menstrual bleeding, prolonged uterine bleeding, and menstrual irregularity), which can cause anemia, pelvic pain, and infertility [2]. When symptomatic, it can have a significant impact on a woman's quality of life and productivity in the labor market (Figs. 6.1, 6.2, 6.3, 6.4, 6.5, and 6.6).

Fig. 6.1 Small submucous myoma

6.2 Abnormal Uterine Bleeding and Fibroids

Among the various complaints associated with uterine fibroids, abnormal uterine bleeding (AUB) is the most frequent and can reach 30% of patients.

The bleeding caused by the uterine fibroid tends to occur in the menstrual period, increasing the flow or prolonging the menstrual period. Intermenstrual and postmenopausal bleeding are more related to other types of uterine diseases, and proper investigation should be performed.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_6) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_6

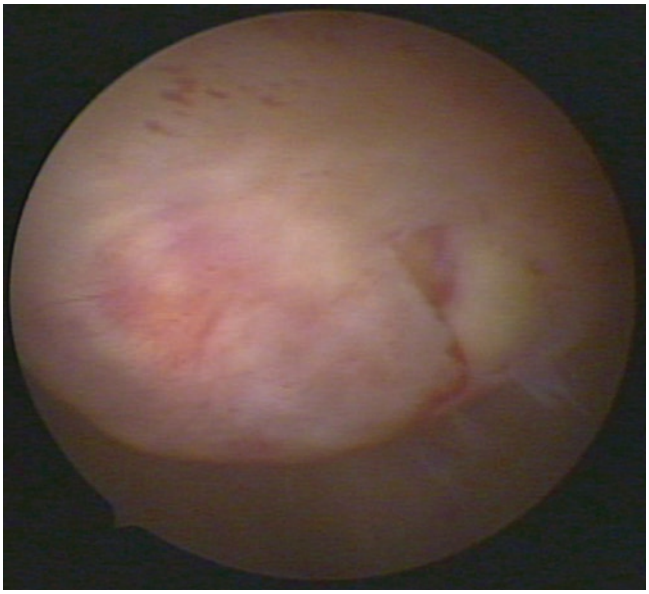

Fig. 6.2 Fundus submucous myoma

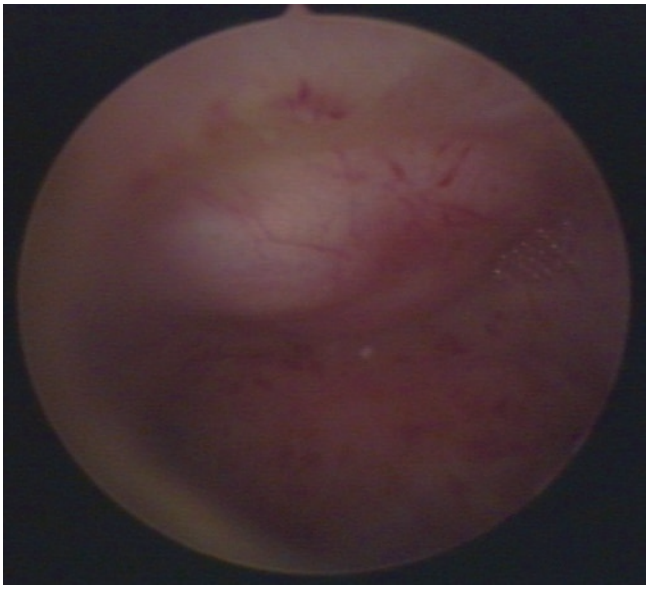

Fig. 6.4 Myoma at anterior wall with intramural component

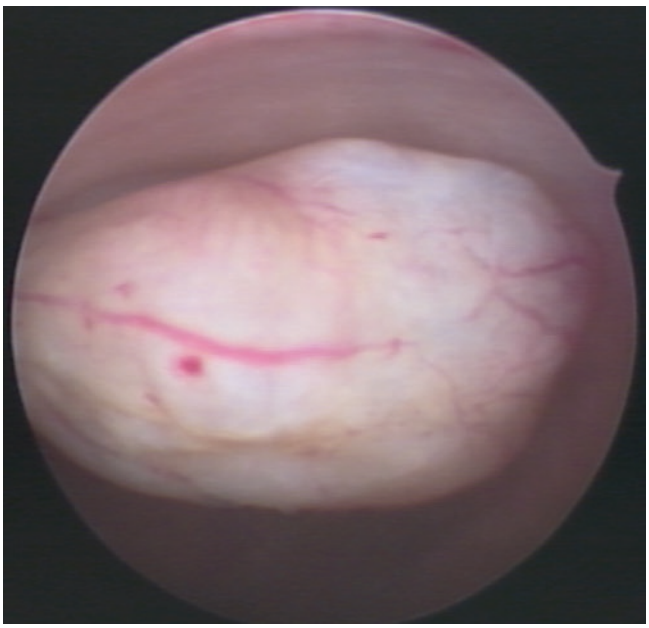

Fig. 6.3 Myoma at anterior wall

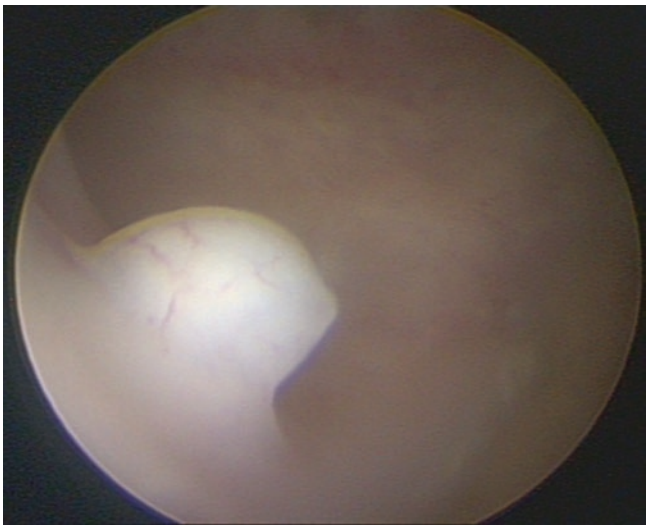

Fig. 6.5 Myoma at posterior wall

In 1956 Jacobson and Enzer described the correlation between submucous myoma and AUB, demonstrating that submucosal myomas were found in 57% of SUA cases [3].

The number and size of these fibroids, as well as their location, may interfere with the symptoms. It is possible to associate the uterine myoma AUB with some factors [4]:

- Increased endometrial surface
- Increased uterine vascularization
- Change in uterine contractility pattern
- Exposure and ulceration of the surface of submucous myoma
- Degeneration of the myomatous nodule
- Uterine venous ectasia by compression of the venous plexus through the nodules

The presence of the submucosal nodule leads to an increase in the endometrial surface that results in a larger area of desquamation and bleeding. On the other hand, the myoma is not very vascularized, with peripheral vascularizа-

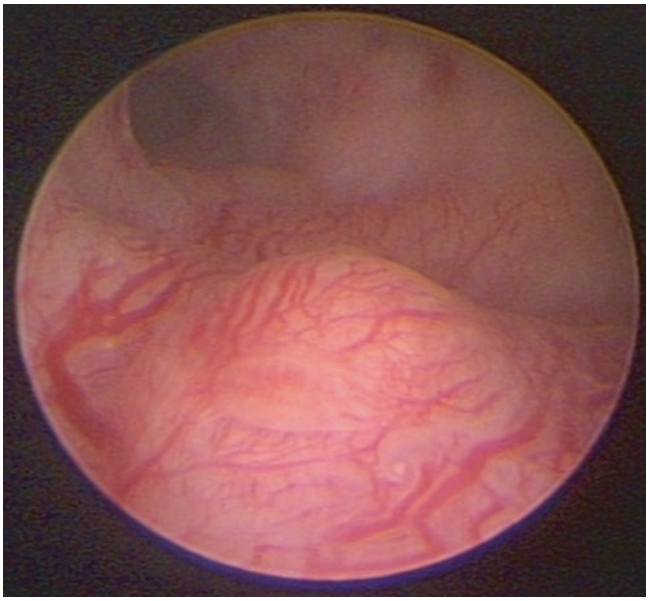

Fig. 6.6 Myoma and vascular aspect

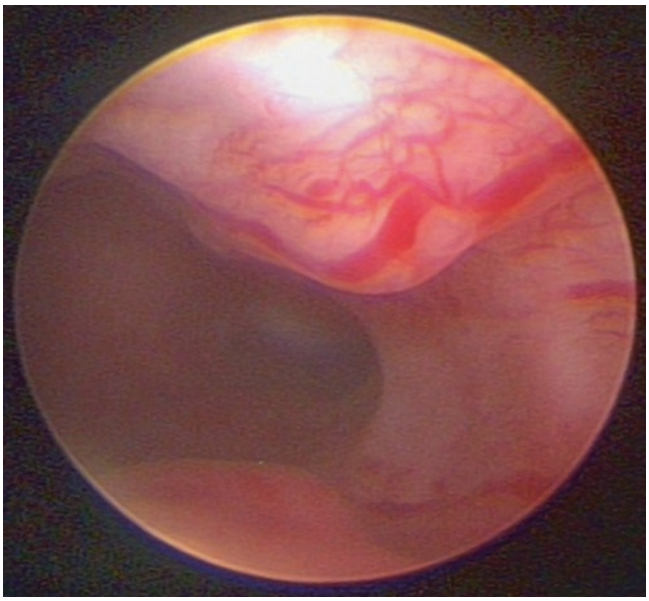

Fig. 6.7 Myoma at anterior wall and vascular aspect

tion, which can cause bleeding by rupturing a vessel from its surface in some cases.

The fibroid, mainly the submucosal, changes the uterine contractility, with interruption of the normal peristaltic movement, important movement for the transport of the spermatozoon in the process of fertilization. This interference in uterine contractility may be associated with AUB, as it prevents adequate hemostasis of the myometrial vessels.

Vascularization of myoma is usually peripheral, and when its growth is greater than the blood supply degeneration and necrosis occur. This process is more frequent in the gestational period, when an accelerated fibroid growth can occur. In some cases, myoma degeneration may expose the vascularization of the nodule, causing abundant transvaginal bleeding [5, 6] (Figs. 6.7, 6.8, 6.9, and 6.10).

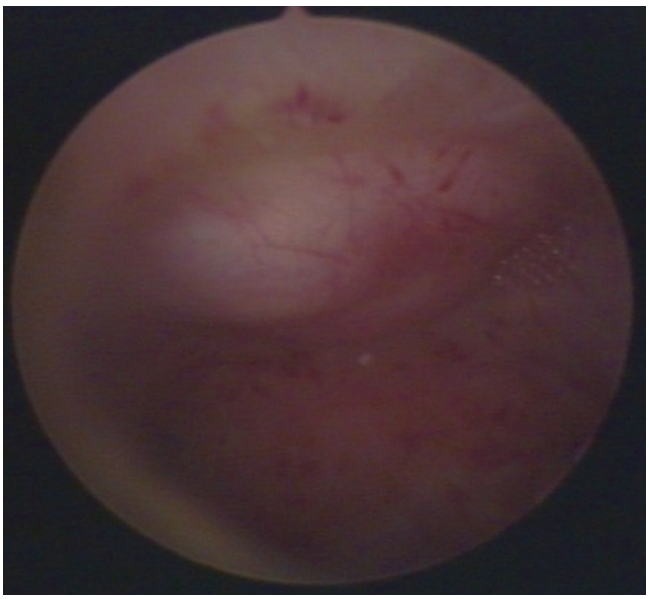

Fig. 6.8 Myoma at anterior wall with intramural component

6.3 Fertility and Fibroids

Uterine fibroids, although very prevalent, are directly related to infertility in only 3–5% of cases. The nodules that most hinder pregnancy or are associated with miscarriages are those with a submucous location. Large or multiple nodules, which lead to significant cavity distortion, or internal orifice obstruction or tubes, can also cause infertility. Hysteroscopy is the method of choice for evaluating the impact of myoma in the uterine cavity, and should be requested in patients with associated infertility (Figs. 6.11, 6.12, 6.13, 6.14, and 6.15).

6.4 Hysteroscopy

Hysteroscopy is the gold standard for identification and definition of the submucosal nodule approach, as well as making it possible to evaluate the cavity, perceiving any existing distortion.

With hysteroscopy, it is possible to rule out other intrauterine bleeding causes and to perform a pathological study of the endometrium or the lesions identified, so it should be indicated in the investigation of AUB when-

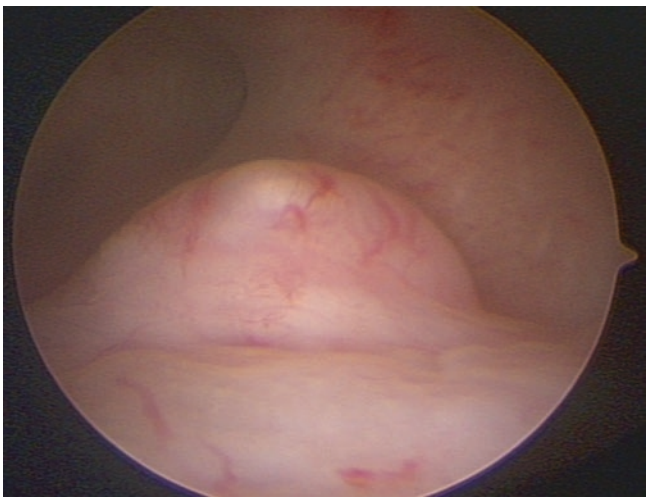

Fig. 6.9 Myoma at posterior wall

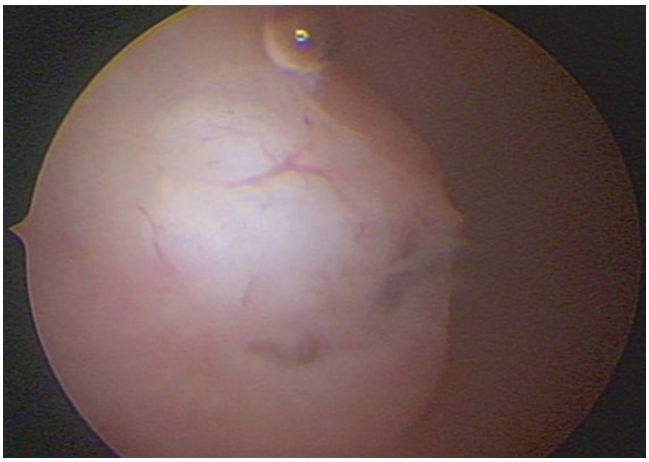

Fig. 6.10 Myoma recovered by endometrium

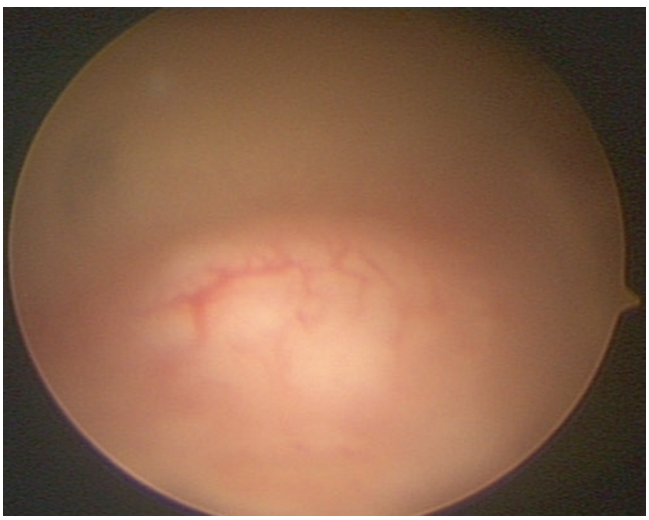

Fig. 6.11 Type 2 Myoma

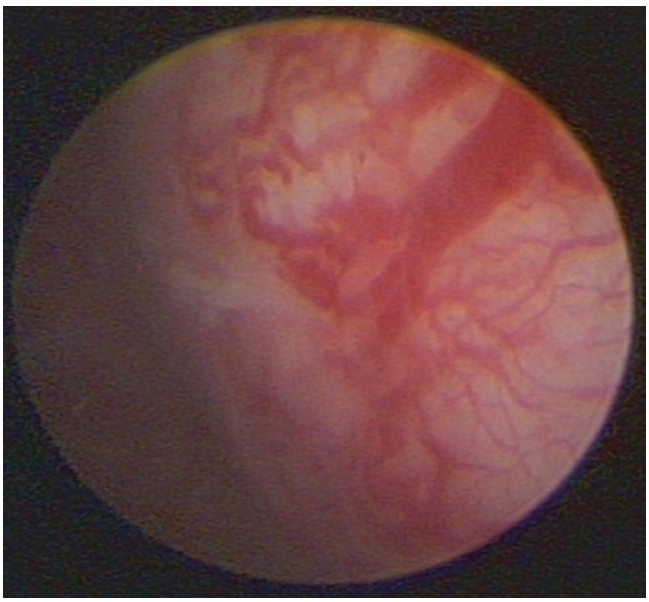

Fig. 6.12 Myoma with superficial vascularization

Fig. 6.13 Pedunculated submucous myoma

ever possible. In the evaluation of postmenopausal patients with uterine bleeding, with or without myoma, investigation of the uterine cavity is mandated by hysteroscopy or by uterine curettage when the first option is not available.

The fibroids that cause AUB have, for the most part, surgical indication and for the evaluation of the difficulty or possibility of hysteroscopic myomectomy, they should be classified. The European Society for Gynecological

Fig. 6.14 "Saturn" submucous myoma

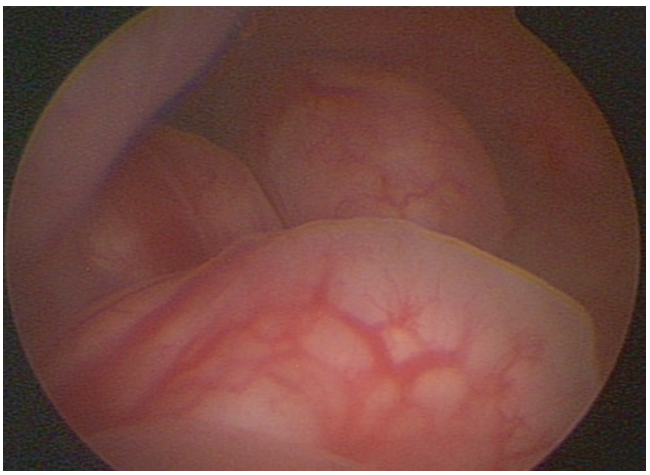

Fig. 6.15 Several submucous myoma together

Endoscopy (ESGE) describes submucous myoma at three levels as described below:

- **Type 0**: fully localized in the uterine cavity
- **Type 1**: with its largest portion located inside the uterus
- **Type 2**: with its smallest portion in the uterine cavity

Another classification, STEPW [7], makes possible the prior orientation to the surgery regarding the possibility, complex or not, or the impossibility of hysteroscopic myomectomy, based on five parameters: size, topography, extension of the base, penetration, and wall (Figs. 6.16, 6.17, 6.18, 6.19, 6.20, 6.21, 6.22, 6.23, and 6.24).

Fig. 6.16 Type 0 Myoma

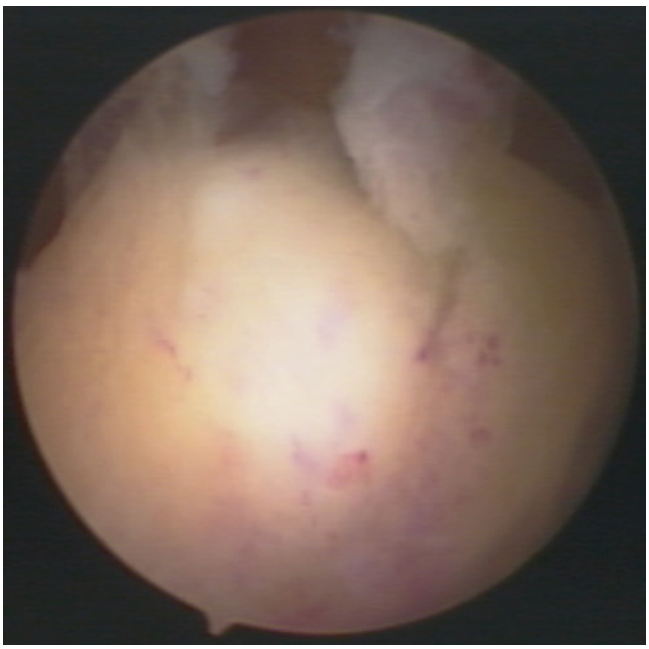

Fig. 6.17 Myoma recovered by endometrium

6.5 Hysteroscopic Myomectomy

Submucosal nodules that are symptomatic or associated with infertility should be approached preferably by hysteroscopy. In patients with a desire for maintenance of fertility, with indication of laparotomy or laparoscopic myomectomy, if they present submucous myoma, the hysteroscopic route

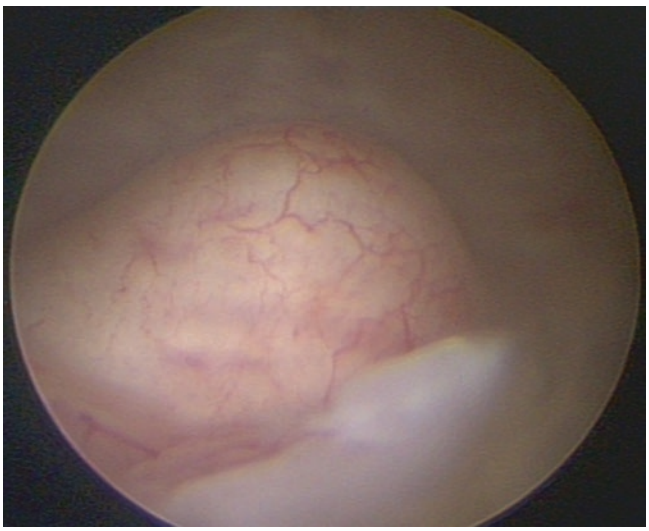

Fig. 6.18 Type 1 posterior wall myoma

Fig. 6.20 Myoma and its peripheral vascularization

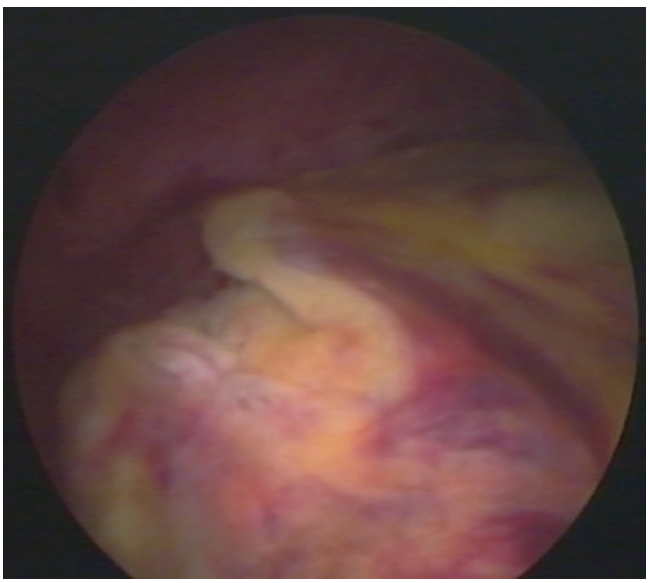

Fig. 6.19 Myoma and degeneration

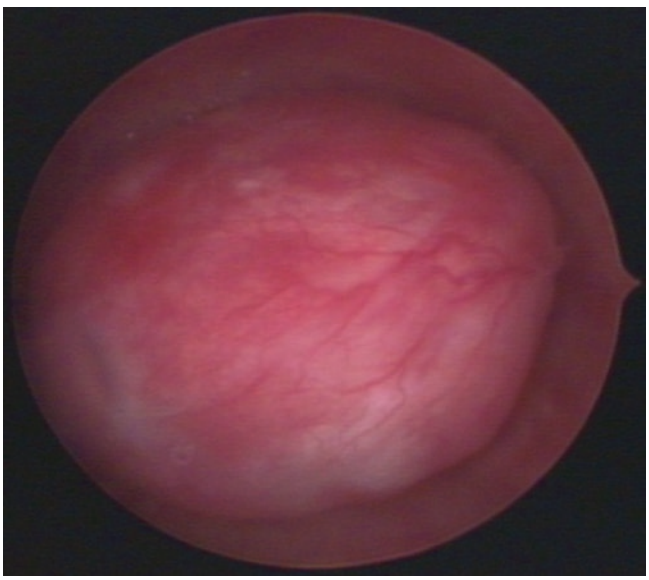

Fig. 6.21 Type 0 fundus Myoma

must be associated with the removal of the myoma, with a better result for reproductive effect.

Hysteroscopic myomectomy can be divided into outpatient or hospital settings. The first, without sedation, is restricted to fibroids up to 3 cm, with little penetration in the myometrium (type 0 or 1). Outpatient hysteroscopic surgery, such as myomectomy, has the following advantages: immediate treatment of the lesion at the same time of diagnosis, reduction of the patient's concern (as well as complaints), lower cost compared to surgery in the hospital setting, and, to the hysteroscopist, the pleasure of performing the best art of hysteroscopy (Videos 6.1, 6.2, and 6.3).

A biopsy punch or scissors is used to access the plane of the pseudocapsule and, with the hysteroscopic sheath, the protrusion of the nodule and dissection of the plane are done. At the end, the nodule is released into the cavity and can be fragmented or withdrawn in full with grasping forceps (Videos 6.4, 6.5, and 6.6).

In cases of difficulty in withdrawing the loose nodule from the cavity, the patient may be advised to return in 7–10 days, during which time the patient is spontaneously expelled (who must be advised of this possibility) or it is drastically reduced of size, facilitating its withdrawal. Currently we have the mini-resectoscope, which allows the use of monopolar or bipolar energy, in an instrument with a final diameter of 16fr (5.3 mm). This instrument allows the resection of polyps and fibroids of larger size, without analgesia, in an outpatient setting, since it allows the fragmentation of large nodules and removal of the entire lesion, with associated hemostasis (Video 6.7).

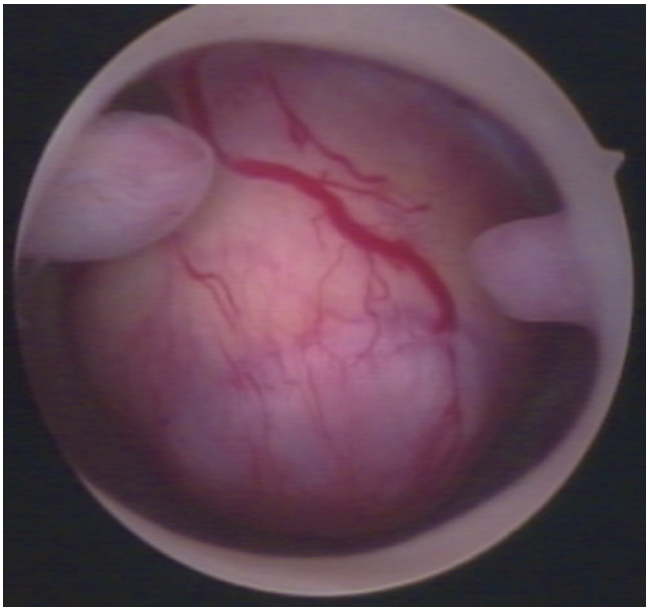

Fig. 6.22 Myoma and polyps

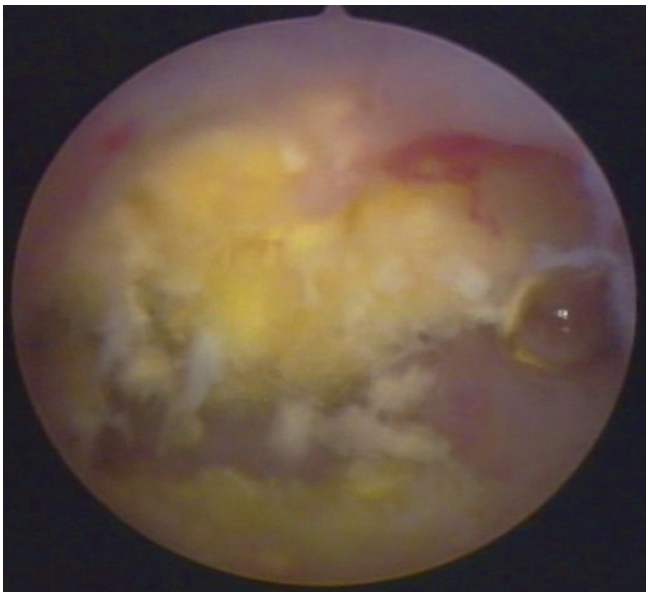

Fig. 6.24 Myoma post embolization

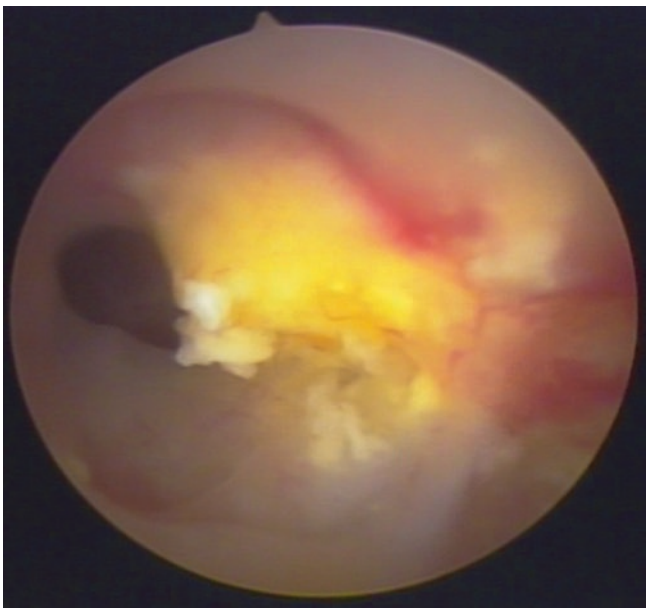

Fig. 6.23 Myoma post embolization

Another technology applied to fibroids is the laser. Under hysteroscopic vision it is possible to "vaporize" the nodule using a laser fiber with a special tip, with excellent results in preliminary studies for submucous nodules and even for large intramural components.

Hospital myomectomy is reserved for larger, deeper nodules or in patients with low tolerance to outpatient procedure. The analgesia of choice for the procedure is blockage (spinal or epidural), and cervical dilatation is necessary for the introduction of a resectoscope.

The resectoscope, bipolar or monopolar, requires the surgeon's dexterity and skill. The electrode movements must be planned and the angulation of the resectoscope during the actuation of the cutting pedal defines the degree of depth of the resection. The movement of the electrode should always be uterine fundus toward cervix, and never the opposite, under the risk of uterine perforation and need for laparoscopic or laparotomic conversion. Cornual regions are thinner and require extreme caution with resections at these sites. Current uterine perforation requires assessment of the abdominal cavity for lesions of associated bowel loops (Figs. 6.25 and 6.26).

To predict the complexity of hysteroscopic myomectomy, Lasmar et al. developed a preoperative classification. The classification of Lasmar or STEPW makes it possible for the surgeon to stratify the difficulty of the hysteroscopic myomectomy, anticipating surgery with low complexity, medium complexity, or not recommended by this technique. Several parameters are considered and, in the possession of this information, one can predict the expected length of surgery, as well as the degree of difficulty of the procedure.

There are a lot of hysteroscopic myomectomy techniques; the most used is the slicing technique that we've learned from urologists (prostate resection). Prof. Mazzon developed his technique using the myoma pseudocapsule, with cold loop dissection, and really good results.

In 2002 Prof. Ricardo Lasmar developed a variation of Prof. Mazzon technique [8] that also consists of the direct mobilization of the nodule from the development of the pseudocapsule plane. Differently, we perform this technique using the conventional resectoscope. For this purpose, a knife-type electrode or Collins electrode is used to encircle the entire myoma and to reach the pseudocapsule. From this point, the fibroid is mobilized and the fibrous bundles are individualized and sectioned with energy. This technique makes it possible to perform myomectomies in nodules with an extremely thin (3 mm) myometrial mantle

[9, 10] (distance to the serosa) since direct mobilization leads to an increase in this thickness, allowing for the expansion of the myometrium below the nodule. The technique reduces the risk of uterine perforation and overload syndrome. The vessels are cauterized punctually, under direct vision, preserving the endometrium and adjacent myometrium, improving the reproductive result.

After total release of the myoma, it is possible to slice it longitudinally with Collins knife, allowing removal of the myoma in a single piece or in fragments, without risk of overload or myometrial injury, since the nodule is already outside the wall and without any vascularization.

After hysteroscopic myomectomy, it is advised to perform ambulatory hysteroscopy for review in 45–90 days. The cicatricial synechiae that eventually appear after the procedure can easily be dislodged in this period, sometimes even with the simple passage of the hysteroscope.

In difficult cases, like in Group III of Lasmar classification, it is possible to make uterine artery embolization, prior to hysteroscopic myomectomy (Fig. 6.27, 6.28, 6.29, 6.30, and 6.31).

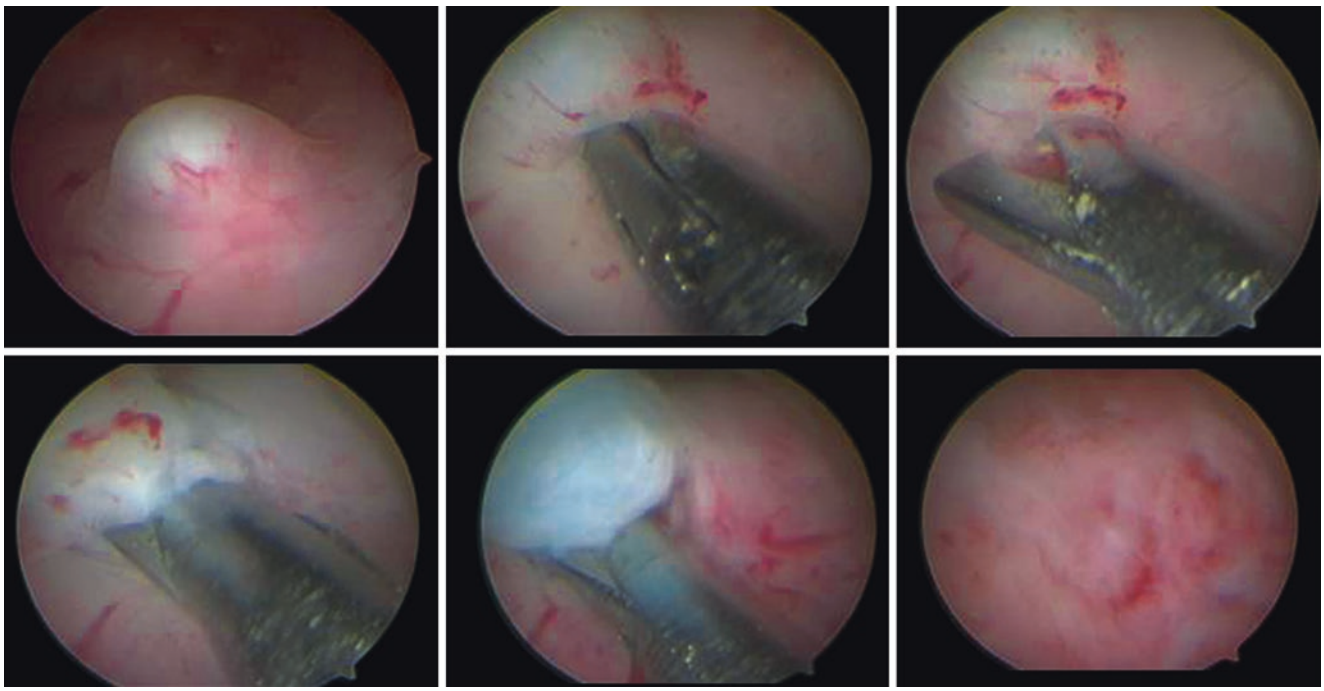

Fig. 6.25 Forceps Office Myomectomy, using pseudocapsule

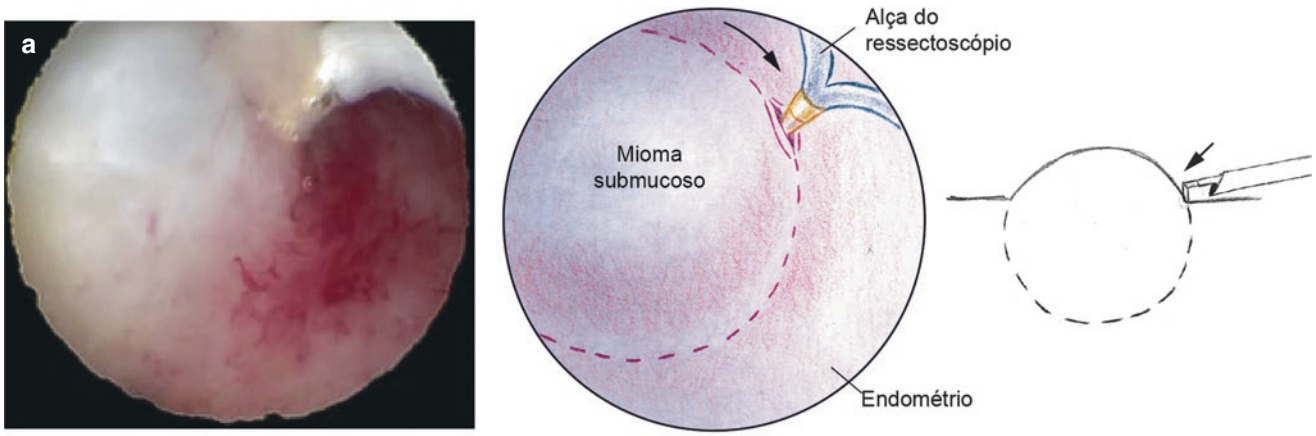

Fig. 6.26 Hysteroscopic myomectomy by mobilization and slicing technique, Using pseudocapsule plane

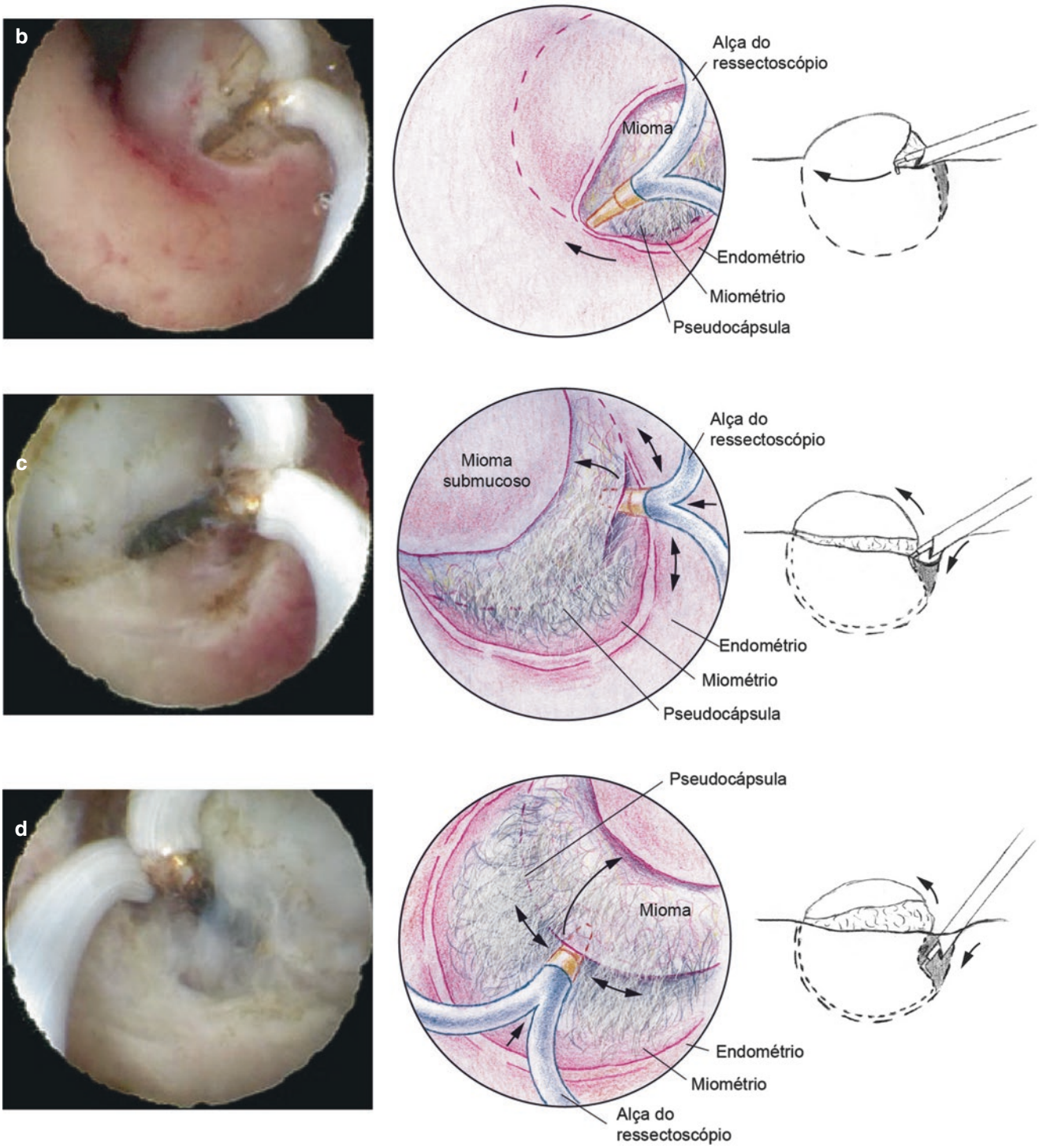

Fig. 6.26 (continued)

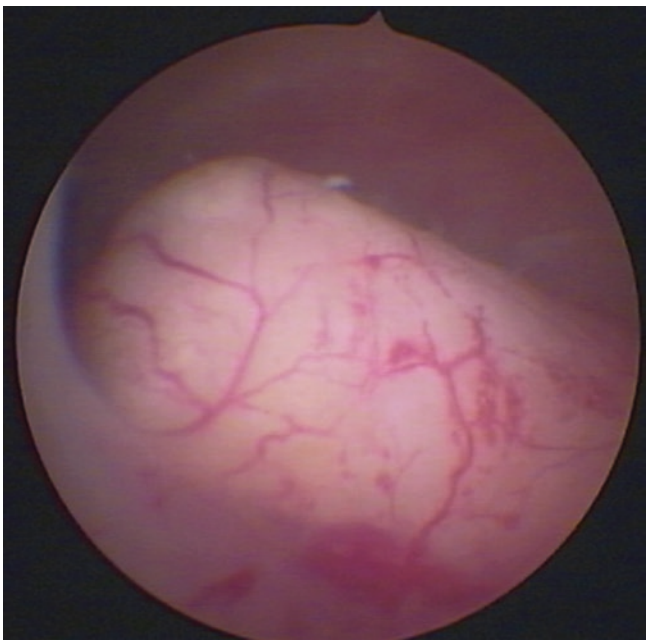

Fig. 6.27 Large basis Myoma

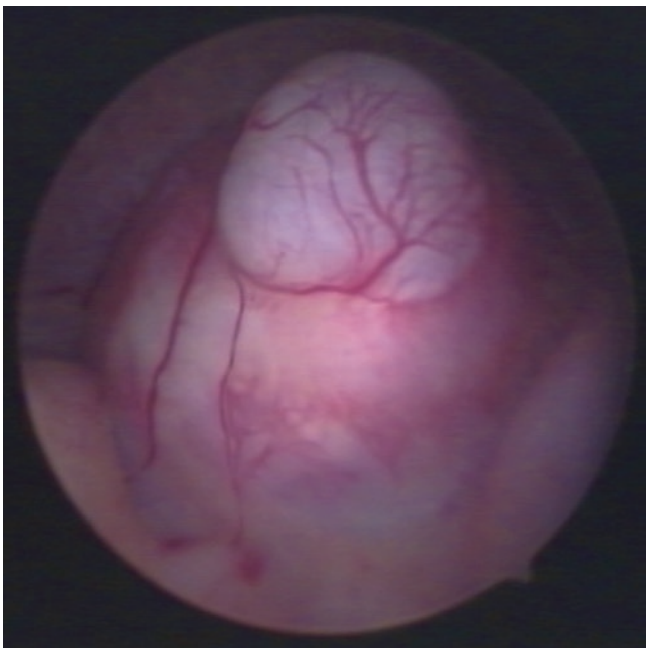

Fig. 6.28 Two myomas together

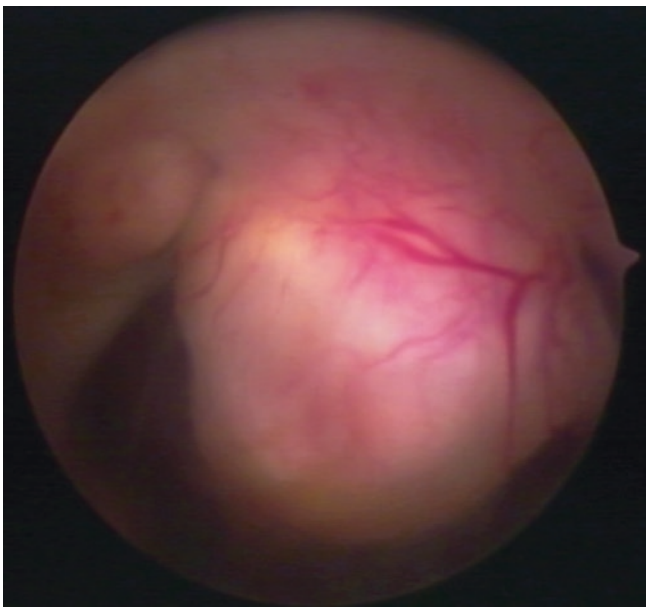

Fig. 6.29 Two myomas together

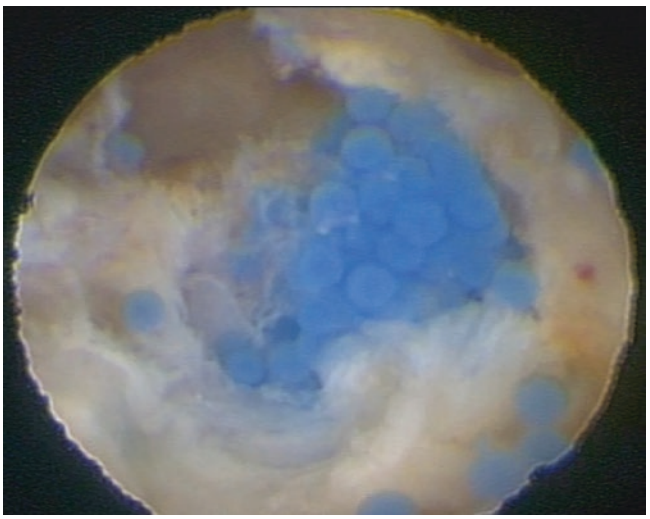

Fig. 6.30 "Embospheres" 6 months after myoma embolization

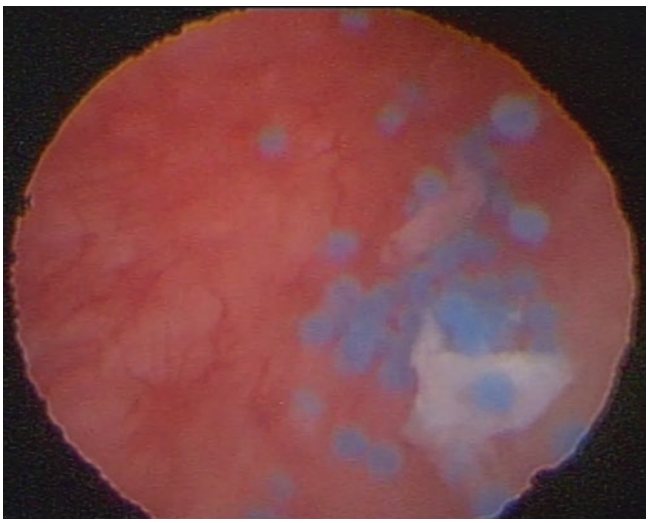

Fig. 6.31 "Embospheres" 6 months after myoma embolization

Acknowledgement *Disclosure of Interest:* The authors have no conflict of interest.

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The Role of Hysteroscopy in Diagnosis and Management of Uterine Anomalies

7

Jaime Ferro, Sunita Tandulwadkar,
Pedro Montoya-Botero, and Sejal Naik

7.1 Diagnosis and Management of Uterine Anomalies

Uterine malformations are the result of a developmental anomaly of the Müllerian ducts or a failure during the fusion [1]. The uterus is formed from the paramesonephric ducts, called Müllerian ducts, at around 8–16 weeks of fetal life. This process encompasses three stages: the organogenesis, or the development of the two Müllerian ducts; lateral fusion, in which the lower part of Müllerian ducts merges and forms the upper part of the vagina, cervix, and uterus; and reabsorption of the septum that is formed after the fusion of Müllerian ducts. This reabsorption begins at 9 weeks of intrauterine life, leaving a single central cavity and cervical canal [2] (Figs. 7.1, 7.2, 7.3, 7.4, 7.5, and 7.6).

Congenital Müllerian anomalies (CMA) have been implicated in women diagnosed with recurrent miscarriage [3, 4]. According to Saravelos et al., the prevalence of CMA in the general population is around 6.7%, whereas in the infertile population is about 7.3% and 16.7% in those women with recurrent miscarriage [3, 4]. However, it is not easy to establish the real incidence of uterine malformations in the general population because most affected women do not present

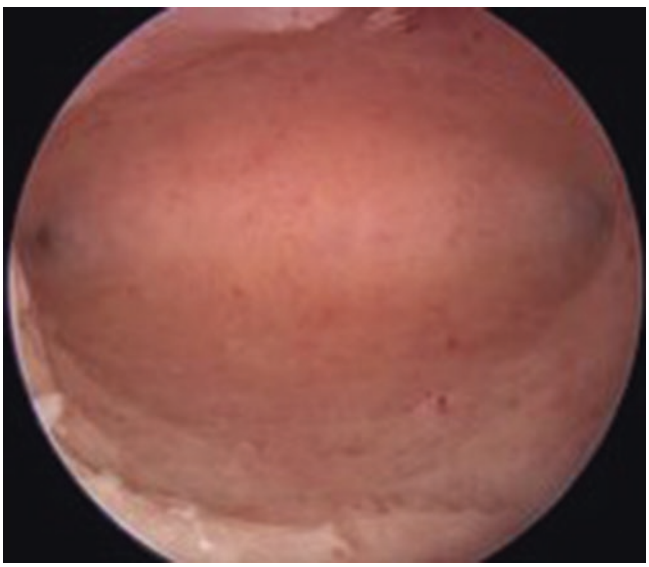

Fig. 7.1 Normal uterine cavity. The normal form of the uterine cavity should be triangular with the small variants depending on the nulliparity or multiparity, from the triangle isosceles to the equilateral. The normal thing is to be able to draw an imaginary diagonal line that goes freely from the isthmic region, immediately above the ICO, to the tubular orifice. The fundus is more or less flat and allows the hysteroscope to pass freely from horn to horn

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_7) contains supplementary material, which is available to authorized users.

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© Springer Nature Switzerland AG 2020
A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_7

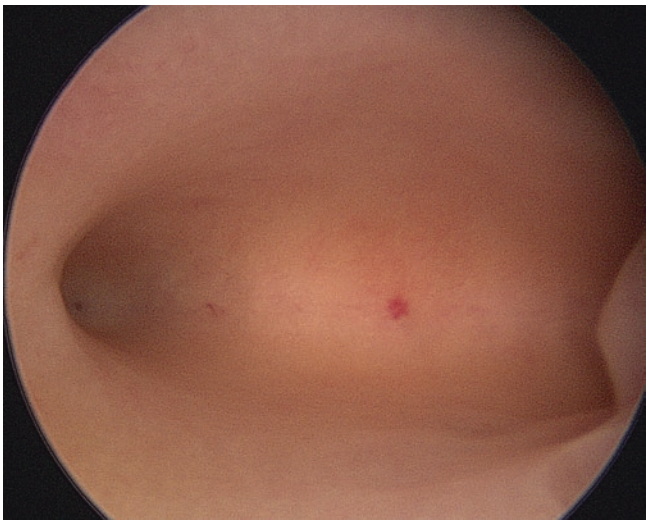

Fig. 7.2 Arcuate uterine cavity. This little anomaly is considered by some as a variant of normally. Correspond to a medial indentation or protuberance like a short septum in the fundus of the cavity that usually does not exceed 1.5 cm. It has been associated with late loss of the gestation. This may be the least of the resorption disorders of the Müller fusion site

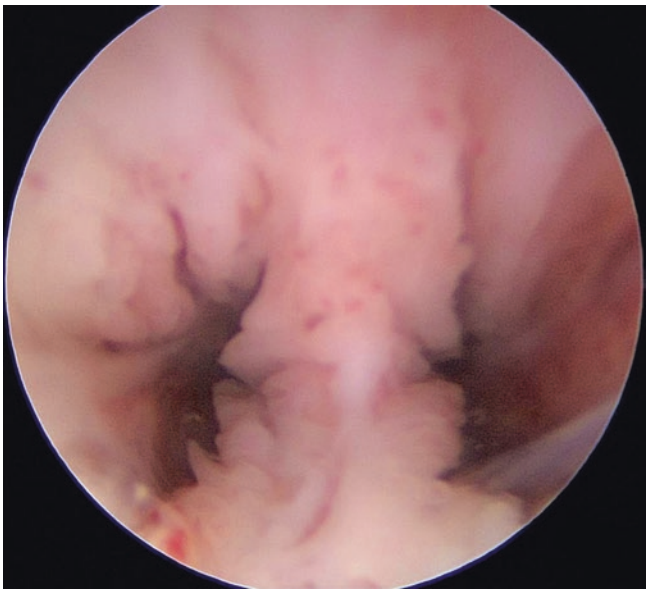

Fig. 7.4 Complete uterine septum. This septum corresponds to the anomaly in which the medial septum of the cavity reaches the internal cervical orifice

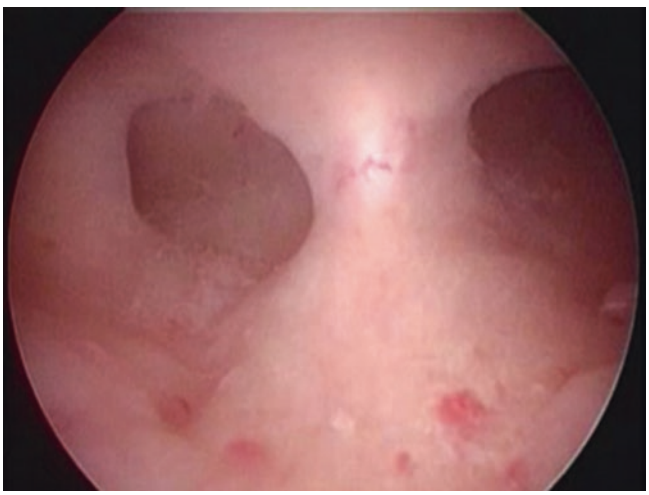

Fig. 7.3 Partial uterine septum. This septum corresponds to the anomaly in which the medial septum of the cavity does not reach the internal cervical orifice. It usually occurs from the middle third but may also be of the upper third and must be differentiated from the cavity with arcuate background

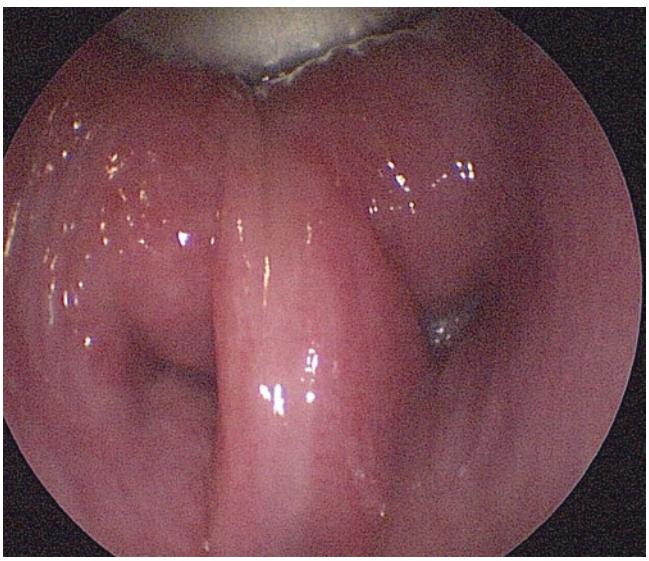

Fig. 7.5 Cervical and uterine septum. This anomaly corresponds to the presence of a uterine cavity septum along with the cervical portion and appears as a simple cervical septum as a double cervix. It can also be accompanied by a vaginal septum

with infertility [5]. Some authors support that the arcuate uterus is the most common form in both fertile and infertile patients. Others claim that the septate uterus is the most common form in those with infertility [2, 6].

Many efforts have been made to design the most appropriate method to classify uterine malformations [5, 7]. The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) created the Congenital Uterine Anomalies Group (CONUTA) with the aim of developing a new classification system of uterine anomalies, based on anatomy, and as simple as possible [8, 9].

Class U0 includes all normal uteri (defined as any uterus having either straight or curved interostial line, but with an internal indentation at the fundal midline not exceeding 50%) [9].

Class U1 (dysmorphic uterus) integrates all uteri with a standard outline but with an abnormal shape of the uterine

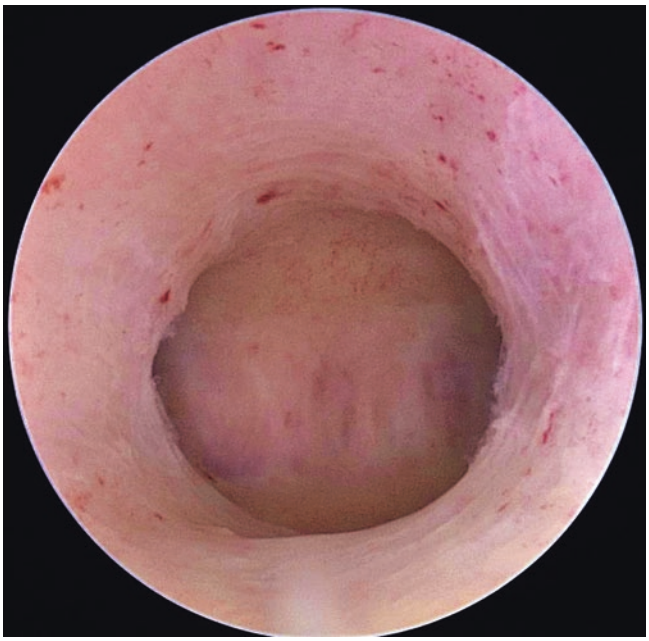

Fig. 7.6 T-shape uterine cavity. The T-shaped cavity shows the prominent sidewalls that give the image of tubular with narrow and deep horns. The fundus has variants, with the most common type being the arcuate or septate. It can also be flat and more rarely slightly biseptate

cavity (excludes septa). Furthermore, class I is subdivided into three categories: class U1a (T-shaped uterus), described by thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix that narrow the uterine cavity. Class U1b (uterus infantilis) is also characterized by a narrow uterine cavity without lateral wall thickening and an inverse correlation (1/3 uterine body and 2/3 cervix). Class U1c (others) was introduced to contain all minor malformations of the uterine cavity [9].

Class U2 (septate uterus) is defined as the uterus with a normal outline and an internal indentation at the fundal midline (exceeding 50% of the uterine wall thickness). Septate uterus is further divided into two subclasses: class U2a or partial septate uterus and class U2b or complete septate uterus [9].

The American Society for Reproductive Medicine (ASRM) proposed their classification in 1988, and it was the most popular and accepted over the last 25 years. This classification included T-shaped uterus into Class VII and associated them with diethylstilbestrol-related (DES) exposure [2, 7, 10, 11].

Recurrent implantation failure (RIF) remains a challenging and extremely disappointing problem for the clinicians and patients, despite the scientific advances in reproductive medicine during the last years [12]. It is defined as failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos (minimum of three fresh or frozen cycles) [13]. Other authors define RIF as the impossibility to achieve conception after 2–6 IVF cycles (with high-quality embryos) [14]. The successful pregnancy outcomes depend on several factors, among which embryo quality and intrauterine environment play significant roles in the achievement and continuation of gestation [15, 16]. Attention has recently focused on the anatomical integrity of the uterine cavity, as a prerequisite for a receptive endometrium [2, 17]. Numerous benign uterine conditions including Müllerian anomalies may explain low pregnancy rates in assisted reproductive technology (ART) [18, 19].

The reason for infertility, although not fully understood, lies in the altered characteristics of the endometrium lining in the malformed uteri, ending in low implantation rates [20]. Several studies have shown that metroplasty (microscissors, electrosurgery, or laser) improves the reproductive outcome of infertile women, independently from the malformation subtype [21–24]. Therefore, it is nowadays considered the first therapeutic option for dysmorphic uteri (compared to abdominal approaches). A recent systematic review and meta-analysis found the presence of congenital uterine anomalies to be associated with a reduced probability of pregnancy (equally in natural and ART cycles). Still, this conclusion only reached statistical significance when summing up both groups [25]. Chan et al., in their systematic review, found diminished fertility outcomes, increased rates of miscarriage, and augmented preterm delivery rates, in patients with dysmorphic uteri (canalization defects). Arcuate uterus (superior third septum) was found to be explicitly associated with second-trimester miscarriage [20].

Some authors recommend metroplasty in patients with recurrent pregnancy loss and premature labor to improve obstetric outcomes. It offers advantages such as shorter operating times and hospitalization period and is considered a safe procedure to perform [22, 24]. However, it is not entirely clear whether hysteroscopic metroplasty, used in patients with RIF and dysmorphic uteri, may improve their reproductive outcomes.

Historically, "T"-shaped uterus was only related to a congenital malformation (DES exposure), yet today we understand that it can also have a primary or an acquired origin (adhesions) [25]. Infertility has been reported to be more common in dysmorphic uteri compared to a normal uterine cavity.

Fedele et al. showed a cumulative pregnancy and birth rates, at 36 months, between 89% and 75%, with 80% in the septate uterus group and 67% in the subseptate uterus group after metroplasty [21]. Correspondingly, other authors have published similar results [25, 26].

In unpublished data from IVI—Valencia, in a group of 190 women, hysteroscopic metroplasty was found safe with no reported intraoperative or postoperative complications and no morbidity associated. Despite there is a lack of consensus on whether infertility is an indication for metroplasty

and the deficiency of prospective, randomized, controlled trials, this procedure has been globally related with satisfactory results in pregnancy and live birth rates.

7.2 Metroplasty

Although the technique may vary between centers, metroplasty is usually performed with a 4.2 mm hysteroscope and a 30° telescope, with an additional external sheath for continuous flow and a 5-French work channel for the use of both scissors and bipolar electrode (Karl Storz, Tuttlingen, Germany). The uterine cavity is distended with normal saline solution (0.9%) at an inflow pressure of 70–100 mmHg. Inflow and outflow fluid volumes are always measured to minimize systemic absorption during surgery and early recognition of excess fluid deficit [27].

The endocervical canal is always inspected at the beginning of the procedure and, once, inside the uterine cavity a systematic examination is performed with a general evaluation of the uterine cavity from the isthmic region. Then, an assessment of the uterine fundus, side walls, anterior and posterior walls, horns, and tubal ostia is always done.

In IVI—Valencia, metroplasty is performed with the usage of microscissors and a high-frequency bipolar electrode and further selective coagulation of bleeding vessels. The surgical procedure consists of performing an incision or straight cuts at the level of the prominent lateral myometrial walls, taking as a guide the nine and three hours from the isthmic region and in the direction towards the tubal orifices. The lateral walls of the cavity are widened, the operation is considered complete when the tubal orifices are seen from the isthmic area of the body, the hysteroscope can be moved freely from one tubal ostium to the other, and a normal uterine cavity of triangular aspect is obtained. Many of these uteri also present some degree of a fundal notch, so they also require remodeling with scissors.

7.3 Postoperative Measures

7.3.1 Prevention of Adhesions

The prevention of intrauterine adhesion (IUA) formation is vital in the treatment of CMA to preserve fertility and to minimize future obstetric complications. For instance, a randomized controlled trial (RCT) reported the risk of IUA in a second-look hysteroscopy, showing incidences ranging from 3.6% after a polypectomy to 45.5% after the resection of multiple myomas [28].

According to a recent prospective study including 163 women undergoing operative hysteroscopy, the time needed for the endometrium to heal completely ranges from 1 to 3 months [29]. In this sense, it is vital to assure the most appropriate adjuvant therapy for at least 1 month while the endometrium heals appropriately.

7.3.1.1 Intrauterine Device

The placement of an intrauterine device (IUD) is one of the most common anti-adherent treatments after hysteroscopy [30]. It may be useful by helping to separate the endometrial layers after surgery, thus preventing adherence formation [31]. Its insertion as an ancillary option for the prevention of IUA has been widely recommended (at least 13 observational studies) [32, 33]. Other authors have proposed that the IUD may provoke a local inflammation reaction with an increased risk of new adherence formation [31]. It appears that both the type and shape of IUD are substantial [34]. Apparently, at the time, there is a need to combine them with one of the alternative therapeutic options available.

7.3.1.2 Foley's Catheter

At least eight observational studies report it as an alternative for the prevention of uterine adherences [32, 33]. Even though it is a straightforward and cost-effective method, there are some concerns regarding the risk of ascending infection from the genital tract, the risk of uterine perforation, and the discomfort produced by its large tubing. Randomized controlled trials, demonstrating the Foley's catheter efficacy in the prevention of AS, are needed.

7.3.1.3 Intrauterine Balloon Stent

Recently, Cook Medical (Cook Medical Inc., Bloomington, USA) introduced a new intrauterine balloon, specially designed to simulate the uterine cavity. The intrauterine balloon stayed in the uterine cavity for around a week (in most studies), to decrease the risk of infection [31, 34]. Despite the results published to date, there is still little evidence on the efficacy of the Cook intrauterine balloon to consider it the best treatment option.

7.3.1.4 Word Catheter

The Word catheter (Cook Medical Inc., Bloomington, USA) is conventionally used for the treatment of abscesses and cysts of the Bartholin gland. It acts as a foreign body, thus preventing the uterine walls to collapse and form adherence. The catheter can remain in position for at least 21 days and up to two menstrual cycles, while the endometrium heals appropriately. However, randomized controlled trials demonstrating the Word catheter efficacy in the prevention of AS will be desirable in the future.

7.3.2 Anti-adhesion Barrier Gels

Hyaluronic acid (HA) is a water-soluble polysaccharide with known viscoelastic properties. The mechanism of action is not entirely understood. However, it works as a mechanical barrier between the uterine walls. It also appears to work in the process of tissue healing by promoting the proliferation rate of the mesothelial cells [31, 34, 35]. One of the newest anti-adhesion barrier gels is the autocross-linked hyaluronic acid (Hyalobarrier©, Fidia Advanced Biopolymers SRL, Padova, Italy). Mais et al., in their systematic review, found it to be useful in the prevention of intrauterine adhesions after surgery [36]. The latest Cochrane review reported no statistically significant differences when using barrier gels [33]. In our experience, Hyalobarrier© is useful, mainly when utilized concomitantly with other therapeutic strategies (i.e., Word catheter, IUD).

7.3.3 Hormonal Treatment

The purpose of the hormonal treatment is to assure the precise re-epithelialization, consequently avoiding the new formation of scar [34].

There is no consensus on whether or not it should be used as a combined or individual treatment (usage of other ancillary therapies); whether it should be used pre- or postoperatively; or whether to combine estradiol with progesterone or for how long [34]. Different studies recommend an estrogen and progesterone treatment following hysteroscopy [32, 33]. However, no good-quality studies have been conducted to examine the ideal combination, duration, or dosage of the treatment [32, 33].

7.3.4 Postoperative Assessment

Even though there is no consensus in the literature, one crucial step in the postoperative management is the "second-look" evaluation. It is capital to re-evaluate the endometrium, to observe the healing process and the scar tissue after surgery [37]. It is imperative to detect newly formed adherences promptly so they can be treated as needed, improving the patient's reproductive prognosis. It should be performed during the early follicular stage of the first or second cycles. Some studies had shown increased obstetric risk and poorer reproductive prognosis when the follow-up was not done [38]. Nonetheless, if not possible, ultrasound or hysterosonography (HSG) is a suitable alternative method.

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Adhesions and Asherman

8

Narendra Malhotra and Jude Ehiabhi Okohue

8.1 Introduction

Intrauterine adhesion or uterine synechiae describes situations where scar tissues develop within the uterine cavity. It was first described and published by a German gynecologist by name Henrich Fritsch in 1894, but became fully characterized by Joseph Asherman in 1948 [1, 2].

It is known as Asherman syndrome when uterine adhesions become associated with symptoms such as menstrual irregularities and infertility. The original definition of Asherman syndrome described pregnancy related trauma to the uterine cavity. Sometimes the same symptoms are present, but the cause of the uterine adhesion is not pregnancy related. While some authors believe the term Asherman syndrome can still be used in such situations, others suggest that it should be restricted to cases of uterine synechiae resulting from endometrial damage related to a gravid uterus [3].

The true prevalence of uterine synechiae is unknown, as the condition is rare in the general population. A prevalence rate of 19.1% was reported by Hooker and colleagues among 912 women, 86% of whom had curettage following a pregnancy loss, with subsequent hysteroscopic assessment of the endometrial cavity [4]. Curettage of a pregnant or recently pregnant uterus therefore appears to be the most common predisposing factor for uterine synechiae. Other causes of uterine synechiae include cesarean section; myomectomy; use of the B-lynch compression sutures; use of intrauterine devices; uterine artery embolization; infections such as tuberculosis of the genital tract; and following surgeries for Mullerian abnormalities [5–7].

The damage to the basal layer of the endometrium results in the formation of granulation tissue on the opposing surfaces of the uterine cavity. Once these coalesce, adhesions form, leading to partial or total obliteration of the uterine cavity.

8.1.1 Classification

A variety of classification systems exist, but no comparative analysis to date has been performed, as comparisons between studies are difficult to interpret.

The European Society for Hysteroscopy classification of intrauterine adhesions is presented in Table 8.1.

Table 8.1 European Society of Hysteroscopy classification of intrauterine adhesions

Grade	Extent of intrauterine adhesions
I	Thin or filmy adhesions easily ruptured by hysteroscope sheath alone, cornual areas normal
II	Singular firm adhesions connecting separate parts of the uterine cavity, visualization of both tubal ostia possible, cannot be ruptured by hysteroscope sheath alone
IIA	Occluding adhesions only in the region of the internal cervical os. Upper uterine cavity normal
III	Multiple firm adhesions connecting separate parts of the uterine cavity, unilateral obliteration of ostial areas of the tubes
IIIA	Extensive scarring of the uterine cavity wall with amenorrhea or hypomenorrhea
IIIB	Combination of III and IIIA
IV	Extensive firm adhesions with agglutination of the uterine walls. Both tubal ostial areas occluded

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_8) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_8

8.2 Diagnosis

The diagnosis of intrauterine adhesion is made based on the clinical presentations and assessment of the endometrial cavity. While some patients have no symptoms, others present with symptoms such as hypomenorrhea or amenorrhea; cyclical abdominal/pelvic pains; recurrent pregnancy loss; and infertility. Hysteroscopy remains the gold standard in the diagnosis of intrauterine adhesions. Hysteroscopy affords the direct visualization of the adhesions and the possibility of treatment (Figs. 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 8.10, 8.11, 8.12, 8.13, 8.14, 8.15, 8.16, 8.17, 8.18, 8.19, 8.20, and 8.21). Hysterosalpingography would show filling defects while at the same time determining the patency of the fallopian tubes (Figs. 8.22 and 8.23). Saline infusion sonography performed in an office setting is equally useful in the diagnosis of intrauterine adhesions. While a versatile sonologist might successfully diagnose intrauterine adhesions using a transvaginal ultrasound scan, magnetic resonance imaging is rarely used due to the exorbitant cost.

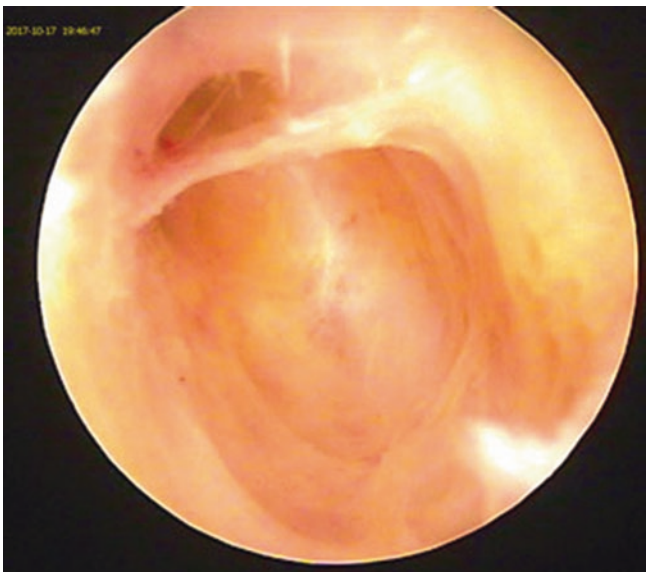

Fig. 8.1 Intrauterine adhesion showing European Society of Hysteroscopy (ESH) classification grade I. This can be broken down with the hysteroscopy sheath

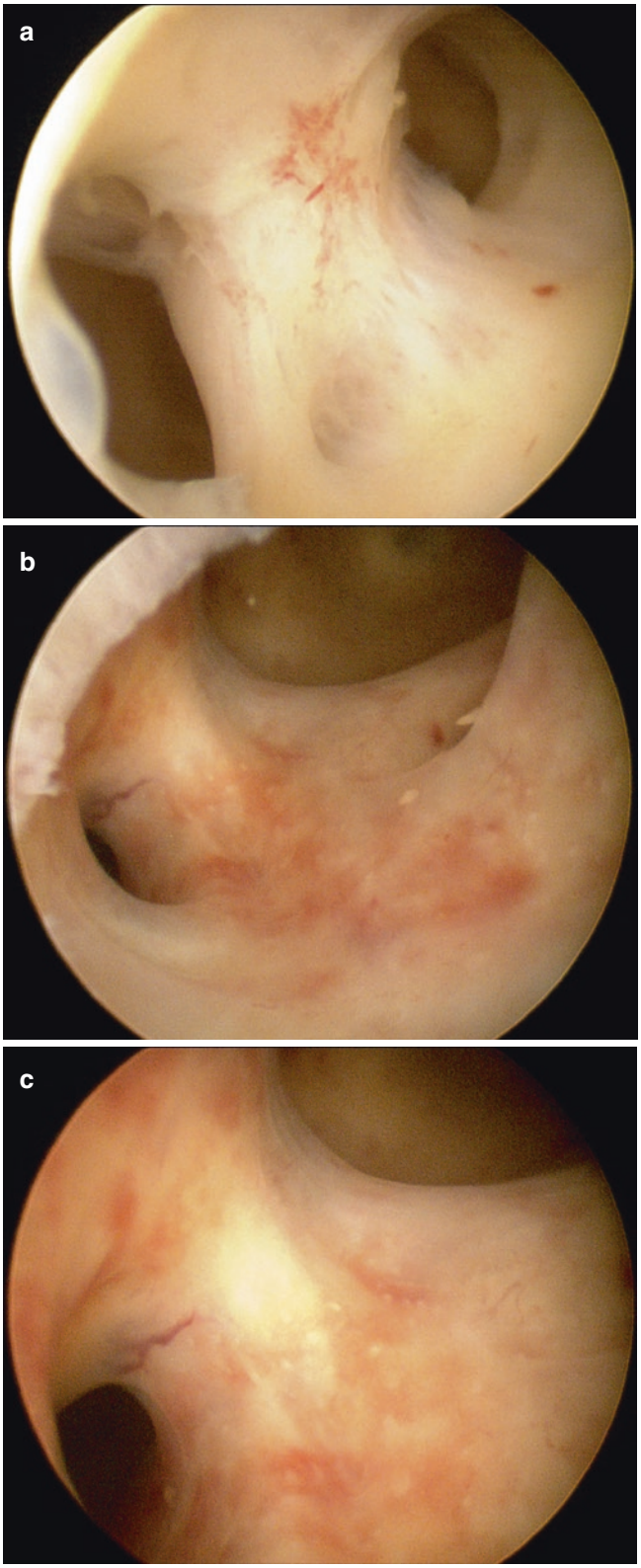

Fig. 8.2 (**a**–**c**) Column of intrauterine adhesions running from the anterior to the posterior uterine walls, ESH classification grade II. See hysteroscopic adhesiolysis in movie 8.1

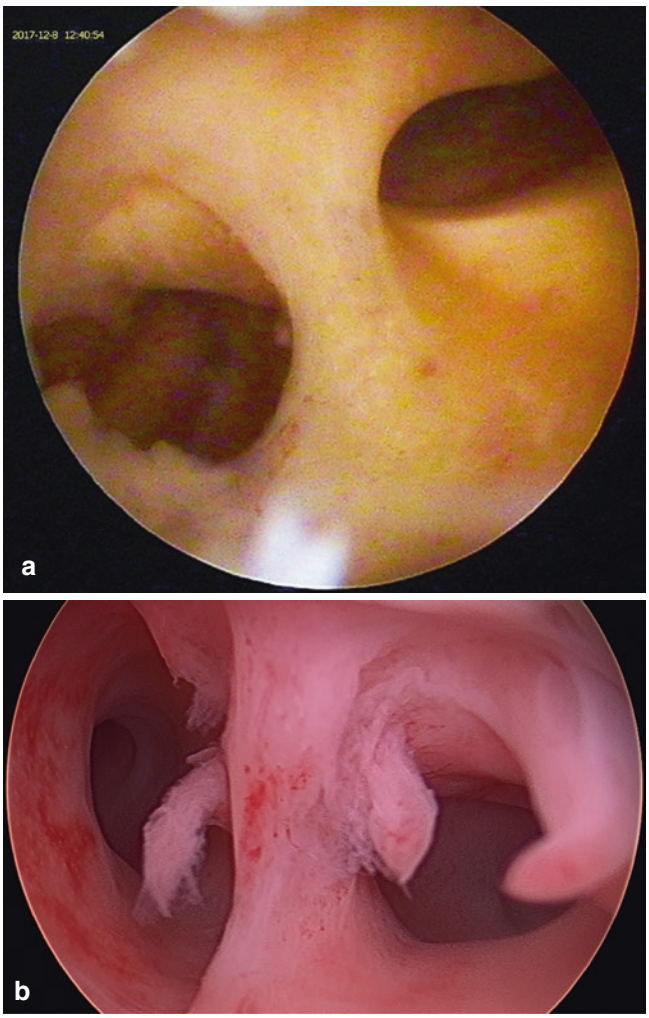

Fig. 8.3 (**a**, **b**) Two more cases of ESH grade II

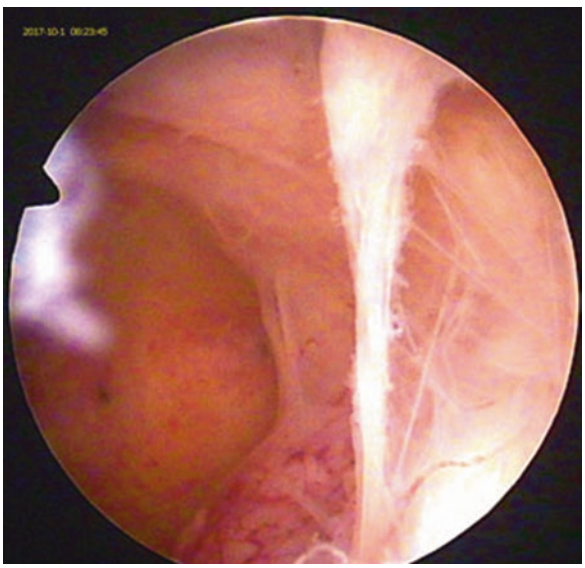

Fig. 8.4 Intrauterine adhesions with associated submucous fibroid

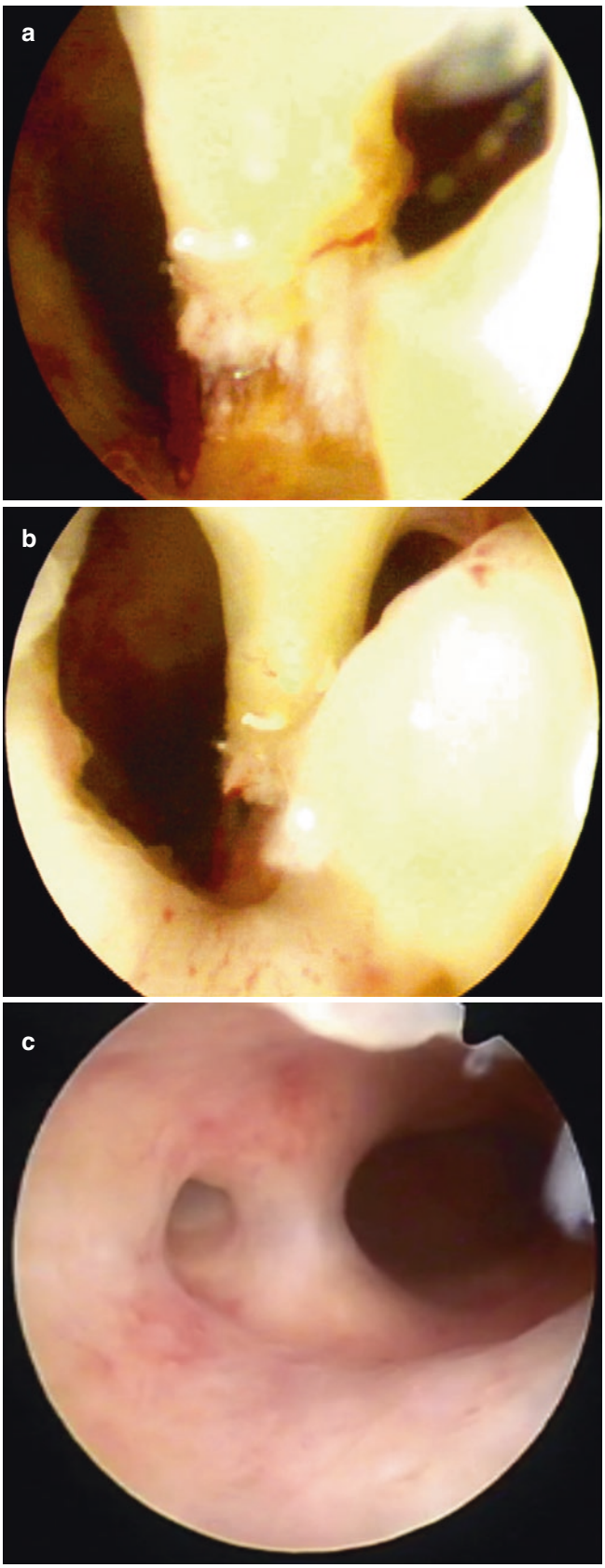

Fig. 8.5 (**a**–**c**) Intrauterine adhesions at the level of the internal cervical os (ESH classification grade IIa)

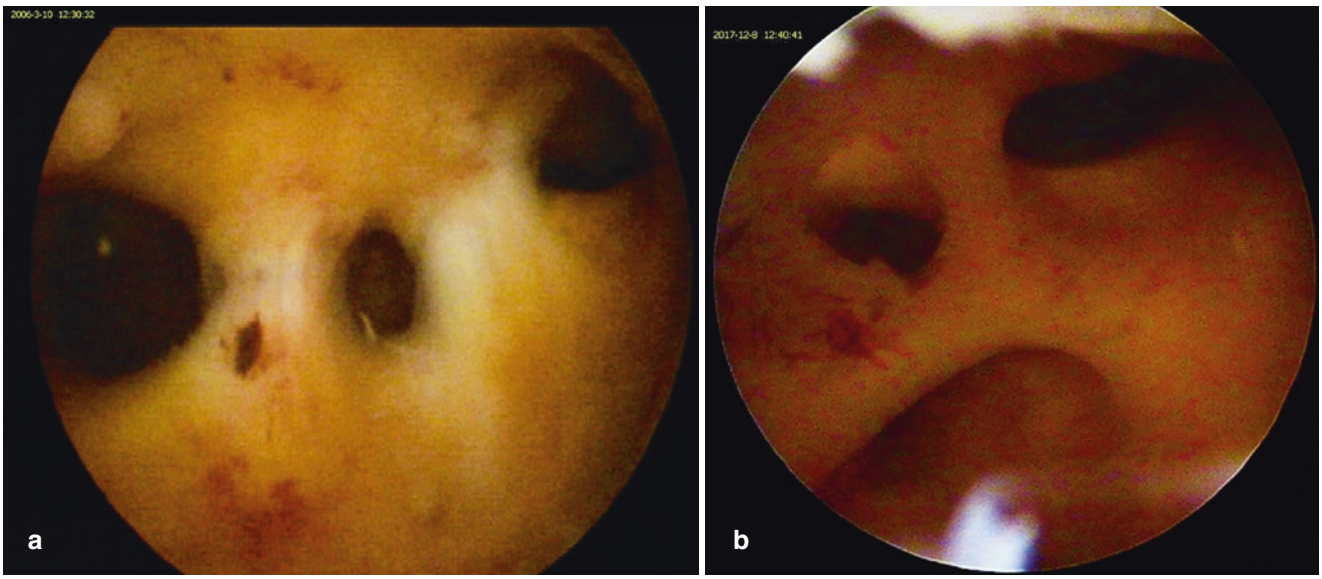

Fig. 8.6 (**a**, **b**) Multiple intrauterine adhesions following abdominal myomectomy

Fig. 8.7 Intrauterine adhesions showing almost complete obliteration of the uterine cavity (ESH classification grade III)

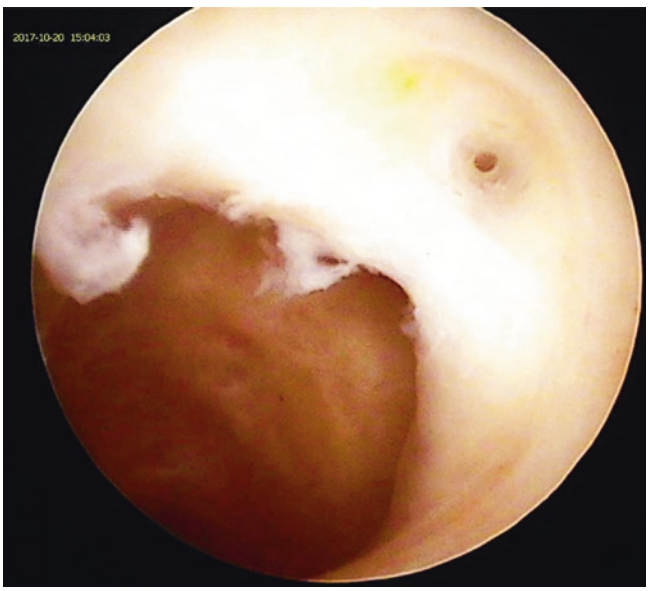

Fig. 8.8 Another case of intrauterine adhesions

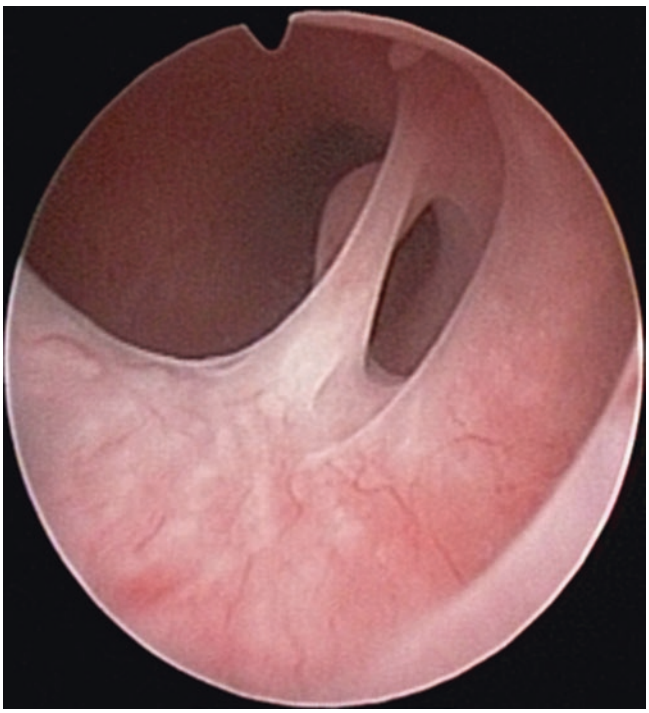

Fig. 8.9 Intrauterine adhesions courtesy of Luis Alonso

Fig. 8.11 Severe intrauterine adhesions (ESH classification grade IV)

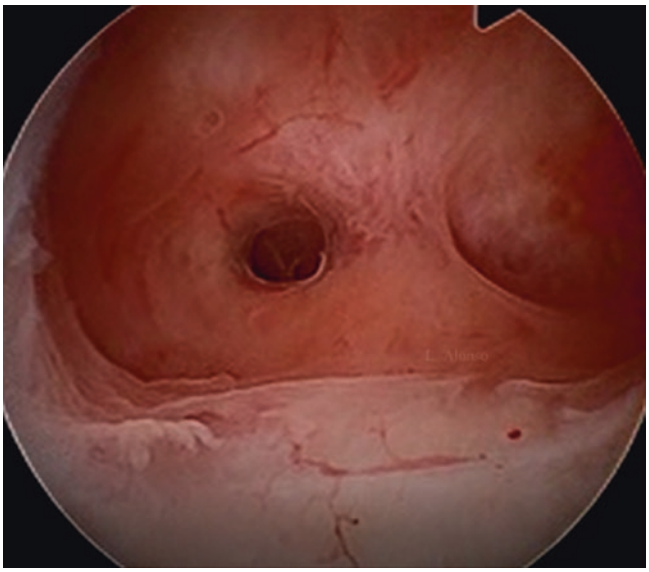

Fig. 8.10 Intrauterine adhesions courtesy of Luis Alonso

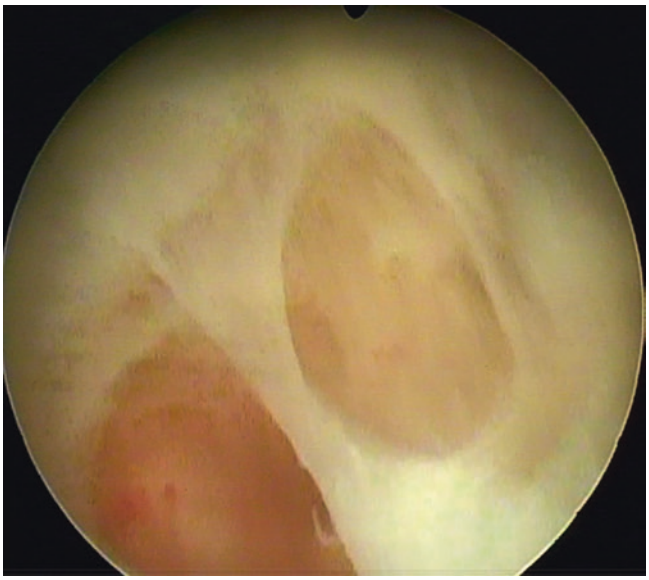

Fig. 8.12 Intrauterine adhesions

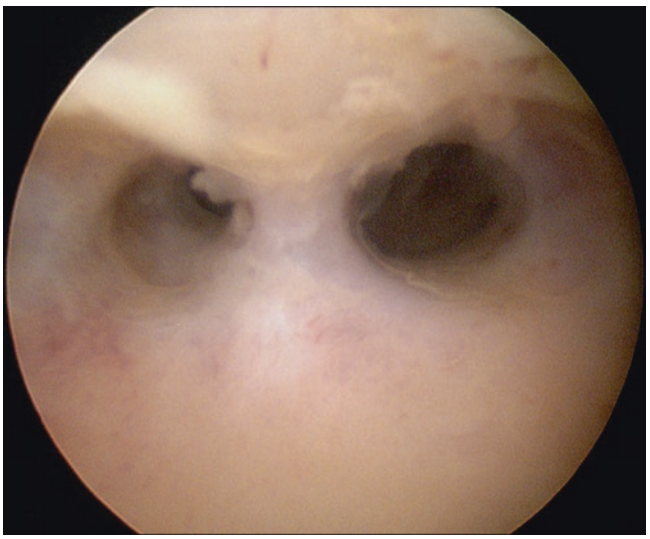

Fig. 8.13 Short column of intrauterine adhesions

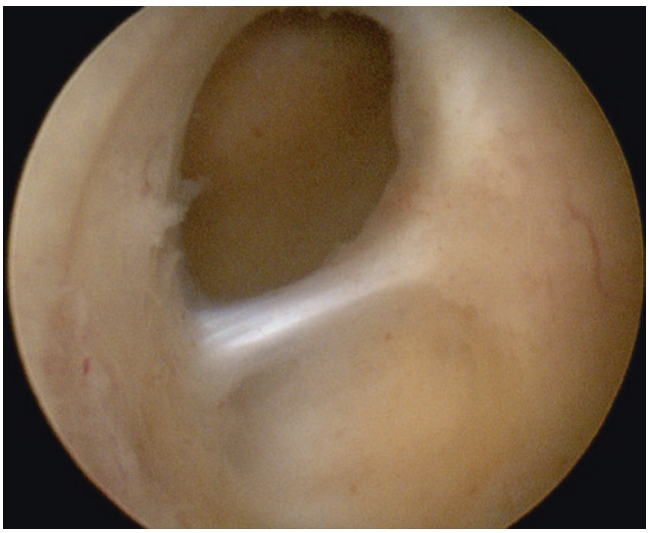

Fig. 8.15 Intrauterine adhesions

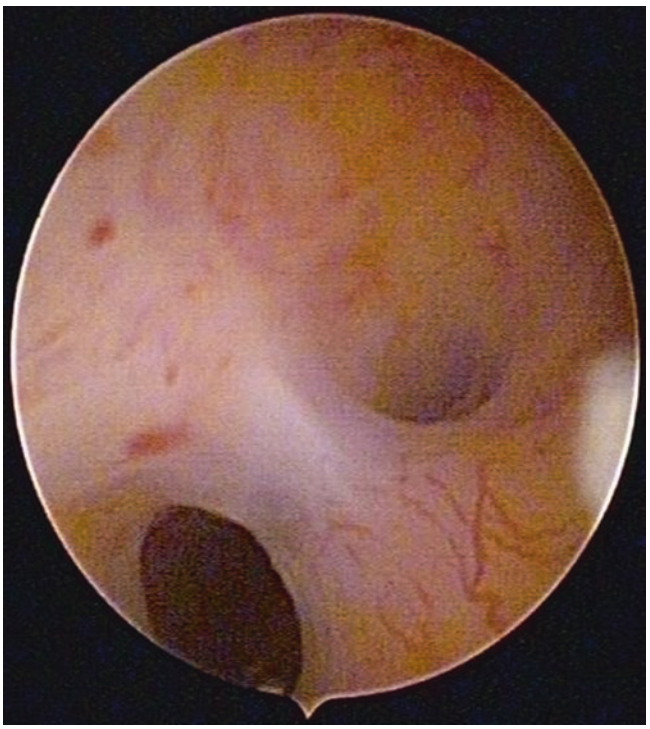

Fig. 8.14 Intrauterine adhesions. Courtesy of Prof. Sergio Haimovich

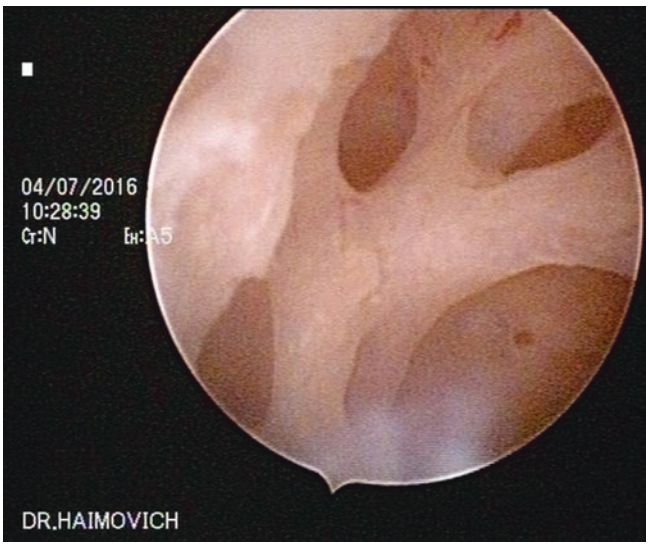

Fig. 8.16 Criss-crossing intrauterine adhesions. Courtesy of Prof. Sergio Haimovich

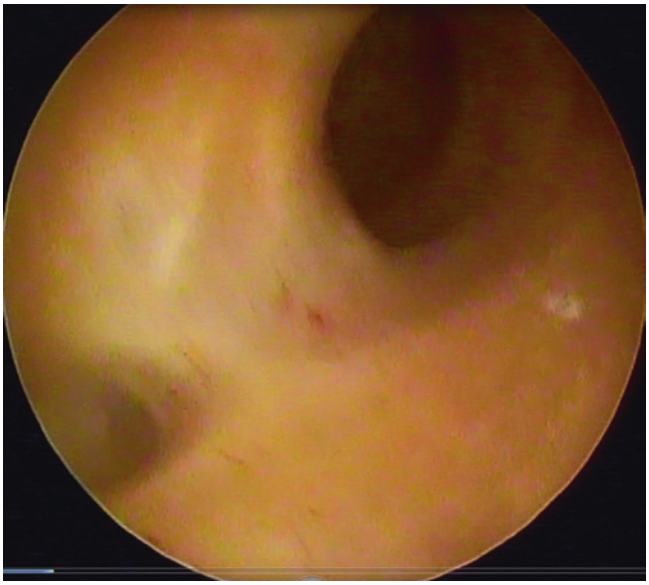

Fig. 8.17 Intrauterine Adhesions

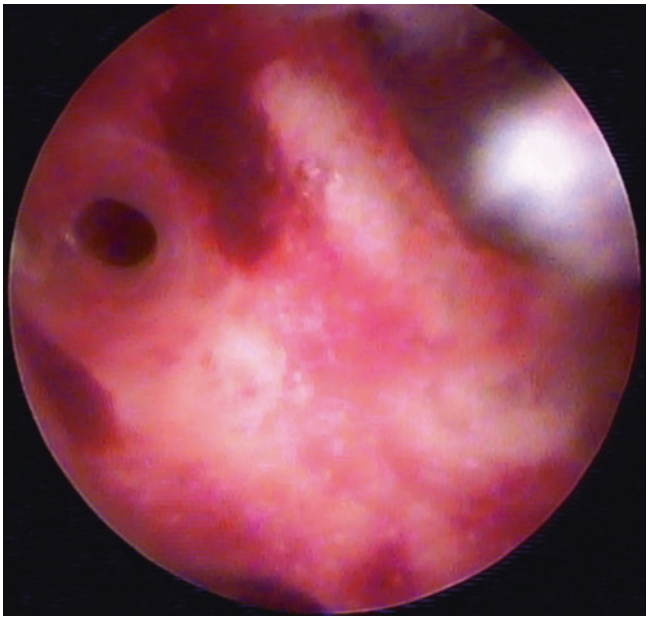

Fig. 8.19 Intrauterine adhesions masquerading as normal fundus and tubal ostium. A normal fundal wall was discovered following adhesiolysis

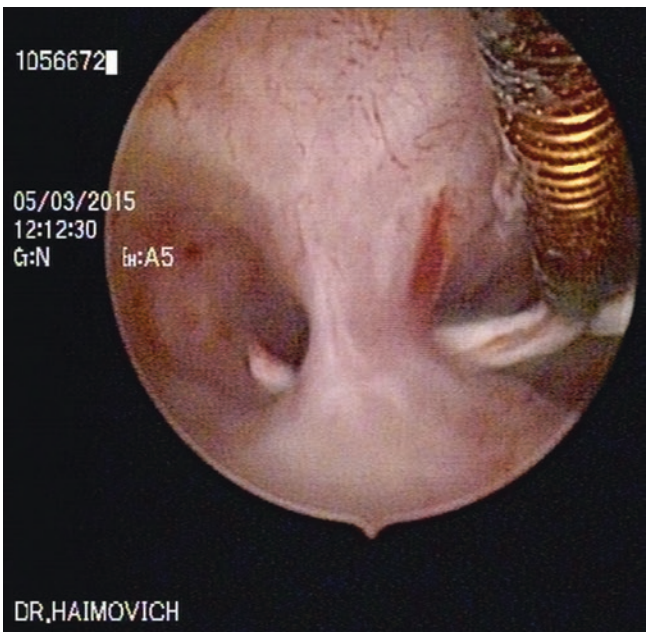

Fig. 8.18 Intrauterine adhesions with an intrauterine device. Courtesy of Prof. Sergio Haimovich

Fig. 8.20 Intrauterine adhesion

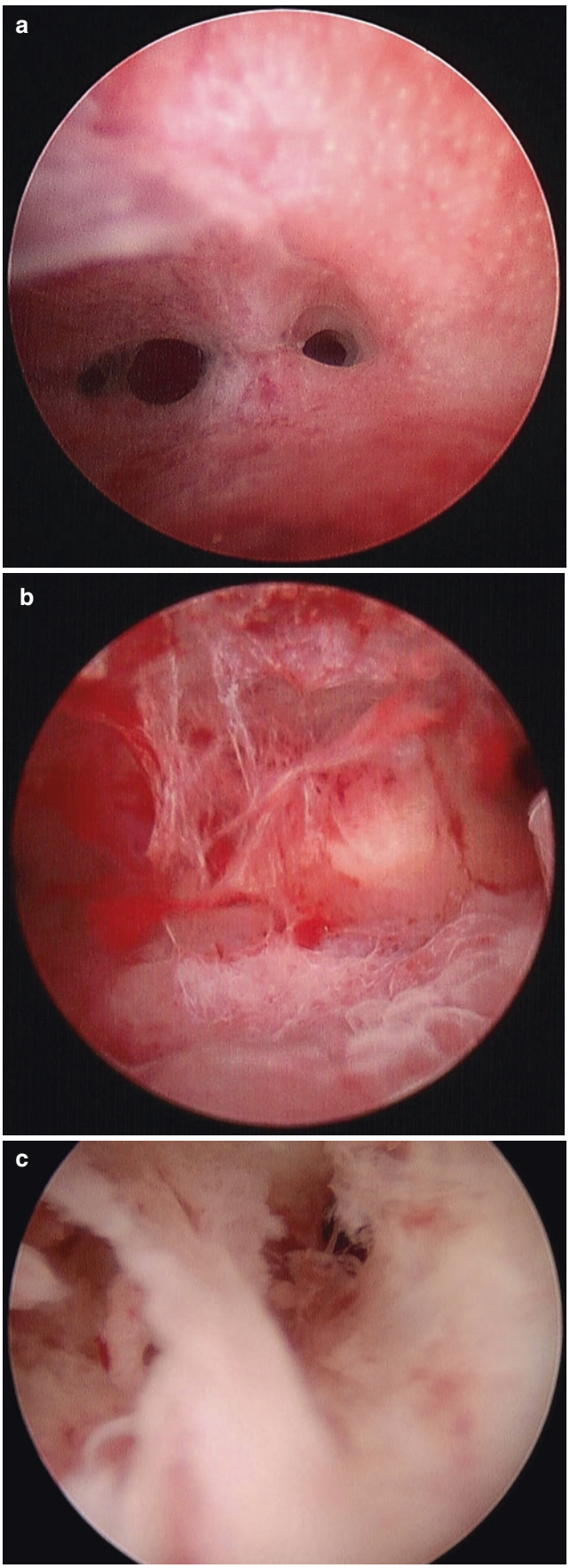

Fig. 8.21 (**a**–**c**) Tuberculous endometritis with intrauterine adhesions. Courtesy of Dr. Sunita Taldudwadkar

Fig. 8.22 Hysterosalpingogram showing multiple filling defects secondary to intrauterine adhesions: Movie 8.2 shows the hysteroscopic assessment and treatment of the patient

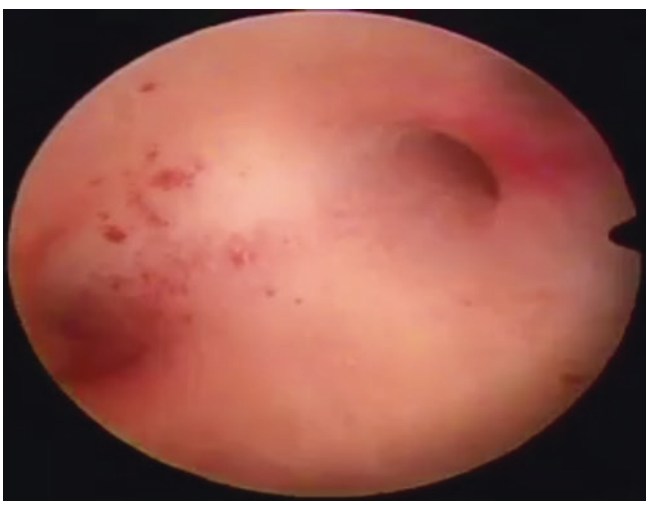

Fig. 8.23 Same patient as in Fig. 8.22 above showing a 'curtain" of adhesion masquerading as a normal fundal wall. Movie 8.2 showcases the hysteroscopic assessment and treatment

8.3 Treatment

Since the advent of hysteroscopy which allowed a proper visualization of adhesions within the endometrial cavity, blind adhesiolysis has been relegated [8]. The treatment of uterine synechiae is aimed at restoring the normal anatomy of the uterine cavity. It also aims at preventing any recurrence. Treatment is based on the personal experience of the gynecologist, case reports, and case series, as randomized controlled trials comparing different treatment modalities are lacking.

A rigid hysteroscope is used for the treatment of uterine synechiae. Commonly used hysteroscopes are the 2.7–4 mm telescopes. Hysteroscopes of less than 2 mm diameter are currently available with good quality of vision. Mild adhesions can be broken with the pressure effect of the distention fluid or with the tip of the hysteroscope [9]. Hysteroscopic scissors is preferred to the use of an energy source by some gynecologists (Figs. 8.24 and 8.25 and Movies 8.1 and 8.2) as it is believed to cause less injury to the endometrium [10, 11]. With the use of an energy source (Fig. 8.26), there is the choice between monopolar and bipolar cautery, which uses nonelectrolyte-containing fluids (such as 1.5% glycine) and electrolyte-containing fluids (such as normal saline), respectively. Strict assessment and documentation of fluid input and output are essential for patient safety, with a deficit of up to 2 L allowed for normal saline and 1 L allowed for 1.5% glycine. Fluid is delivered either with the manual pressure cuff or with the use of automated pumps.

In terms of technique, the adhesions that are centrally located within the uterine cavity are dealt with first before breaking down those located at the periphery of the cavity [12].

In very severe cases of intrauterine adhesions, the hysteroscopic procedure is carried out under simultaneous ultrasound scan, laparoscopy, or fluoroscopic guidance (Movie 8.3). Despite this, hysteroscopic adhesiolysis still remains the procedure with the greatest risk of perforation of the uterus [13].

Stem cell therapy seems to be gaining popularity in the management of uterine synechiae.

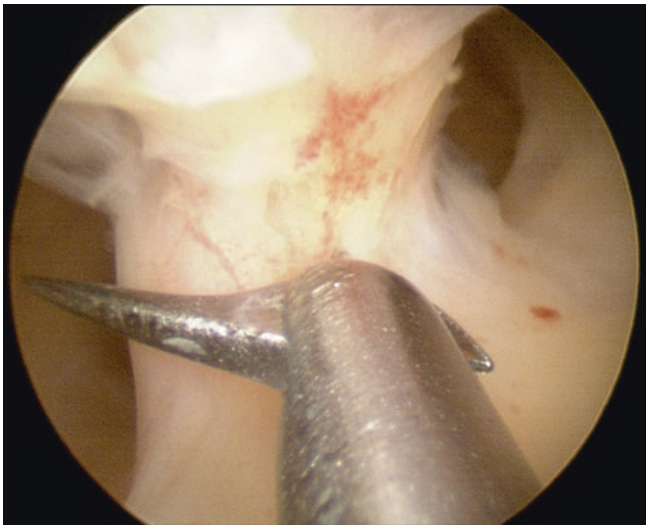

Fig. 8.24 Hysteroscopic adhesiolysis with scissors

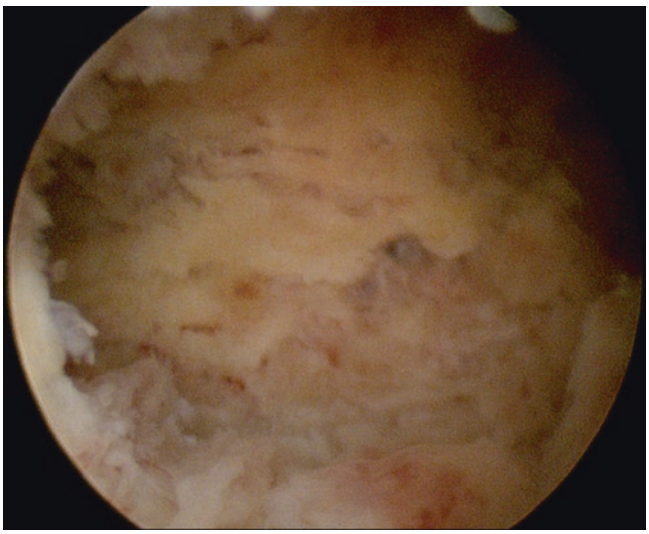

Fig. 8.25 Uterine cavity following hysteroscopic adhesiolysis with scissors

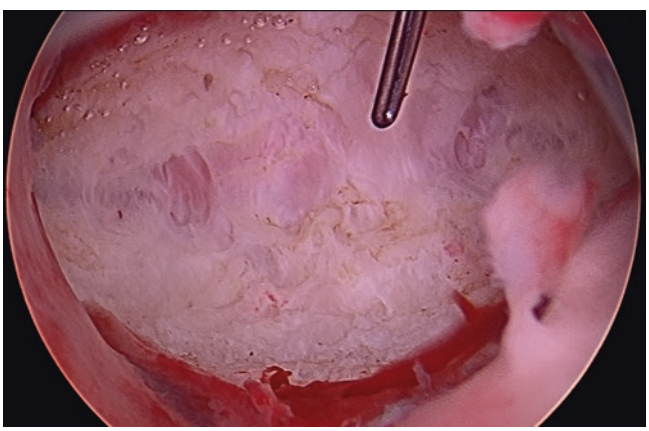

Fig. 8.26 Hysteroscopic adhesiolysis with cautery. Courtesy of Dr. Mykhailo Medvediev

8.4 Prevention of Adhesion Reformation

In the prevention of adhesion reformation, the following have been used:

- Intrauterine device
- Intrauterine Foley catheter
- Intrauterine balloon stent
- Intrauterine gel
- A non-randomized study which compared the use of Foley catheter for 10 days with an intrauterine device for 3 months following adhesiolysis found fewer infections and lower recurrence rate in the Foley catheter group [14].

A high impedance of spiral arteries was observed in patients with Asherman syndrome, and this is suspected to be responsible for the reduced endometrial receptivity and regeneration in women with Asherman syndrome [15]. Estrogens at various dosages have been used with the intention of stimulating endometrial growth after adhesiolysis. Other medications that have been used but not endorsed include aspirin, nitroglycerin, and sildenafil citrate.

Assessment of adhesion reformation can be done via office hysteroscopy, saline infusion sonography, and hysterosalpingography. While mild-to-moderate intrauterine adhesions have a recurrence rate of about 33%, about 66% of patients with severe adhesions would likely develop a recurrence [16].

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9 The Role of Hysteroscopy in the Diagnosis and Management Endometriosis and Adenomyosis: The Current Perspective

Alexandra Garcia, Jose Carugno, and Luis Alonso Pacheco

9.1 Introduction

Adenomyosis is defined as the abnormal presence of endometrial glands and stroma within the myometrial layer of uterus. Symptoms of adenomyosis include uterine enlargement, abnormal uterine bleeding, and dysmenorrhea [1]. Adenomyosis is further categorized depending on the extent of myometrial invasion, including diffuse or local adenomyosis [2]. In diffuse adenomyosis, endometrial glands and stroma are irregularly embedded into the myometrium contributing to a bulky, enlarged appearance of the uterus. In focal adenomyosis, adenomyomas consist of a single nodular aggregate with both solid and cystic components situated within the myometrial layer of the uterus, similar to leiomyomas. The term "cystic" is used in the presence of diffuse adenomyosis or adenomyomas for which cysts are ≥1 cm in diameter. In addition, adenomyomas can resemble leiomyomas not only physiologically but also clinically [3].

Endometriosis is defined as endometrial glands and stroma located in tissue outside the uterine cavity. These lesions are typically confined to the pelvis; however, they may spread and affect multiple other sites including the bowel, diaphragm, and pleural cavity. This ectopic endometrial tissue and its resultant inflammation are direct causes of the symptoms that often characterize this disease including dysmenorrhea, dyspareunia, chronic pain, and infertility [4, 5].

Both adenomyosis and endometriosis represent disorders of ectopic endometrium. In addition, both diseases are direct causes of pelvic pain. Despite this, these two diseases are not otherwise thought to be related.

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9.2 Epidemiology and Risk Factors

9.2.1 Adenomyosis

The natural history and the prevalence of adenomyosis are not well established. A definitive diagnosis can only be made histologically with examination of pathology following hysterectomy, and a clinical diagnosis can be made using imaging studies. It is generally estimated that adenomyosis is present in 20–35% of women [6, 7].

Studies show that adenomyosis has been found to be more common in parous than nulliparous women [8]. The relationship between parity and adenomyosis, however, may be biased since the diagnosis is typically made only at the time of hysterectomy. Interestingly, in women with leiomyomas, parity is associated with a decreased risk of disease.

9.2.2 Endometriosis

The exact prevalence of endometriosis in the general population is challenging to discern because some women are asymptomatic, and the prevalence of endometriosis in symptomatic referral populations appears to be much higher. Endometriosis has been reported in up to 40% of adolescents with genital tract anomalies [9]. It has also been shown in up to 50% of women with infertility [10] and up to 70% of women and adolescents with pelvic pain [11–14].

9.3 Symptoms

Heavy menstrual bleeding, dysmenorrhea, and chronic pelvic pain are the most common symptoms of adenomyosis [8]. Heavy menstrual bleeding is possibly due to the increased endometrial surface of the enlarged uterus, while pain may be secondary to bleeding and swelling of endometrial implants embedded within the myometrium. Symptoms

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_9

typically develop between the ages of 40 and 50 years; however, approximately one-third of women are asymptomatic throughout their lifetime [8]. In contrast with endometriosis, dyspareunia is not a typical symptom. It is controversial whether adenomyosis is linked to infertility.

Most women with adenomyosis have another pathologic process in the uterus that often obscures the diagnosis making the diagnosis of "pure" adenomyosis difficult. According to McEllin et al. [8], it was noted that in 50% of women with adenomyosis, leiomyomas are found. Some studies show that 11% of women with adenomyosis concomitantly develop endometriosis; however, Kunz et al. [15] reported that adenomyosis was suspected on MRI in up to 90% of women with endometriosis. Furthermore, endometrial polyps were present in 7% of women with adenomyosis.

Women with endometriosis classically present during their reproductive years with pelvic pain with associated dysmenorrhea and dyspareunia, infertility, or an ovarian mass [16–18]. Women can also present without having symptoms of endometriosis, and it is incidentally found during surgery or imaging for other indications. While the peak prevalence of endometriosis occurs in women 25–35 years of age [19], the disease affects between 2% and 5% of postmenopausal women [20].

9.4 Diagnosis

The recent evolution of diagnostic imaging techniques has contributed to a more accurate identification of this disease. Transvaginal ultrasound is the first-line imaging choice for evaluation of an enlarged uterus, pelvic pain, and/or abnormal bleeding. Accordingly, the most frequently used imaging modalities consist of transvaginal ultrasound (TVS) followed by magnetic resonance imaging (MRI) which is reserved for those cases in which it is important to distinguish diffuse and focal adenomyosis from leiomyomas and in cases when an accurate diagnosis is pivotal in guiding management approaches. Most recently, the advent of hysteroscopy has played a large role in the diagnosis and treatment of adenomyosis, as it provides the opportunity to perform biopsies.

The following hysteroscopic findings have been suggested as indicative of endometriosis [21]:

1. Irregular endometrium with small defects seen on the endometrial surface (Figs. 9.1, 9.2, and 9.3)
2. Pronounced bulge in endometrial cavity with altered vascularization (Figs. 9.4 and 9.5)
3. Endometrial "strawberry" pattern (Figs. 9.6 and 9.7)

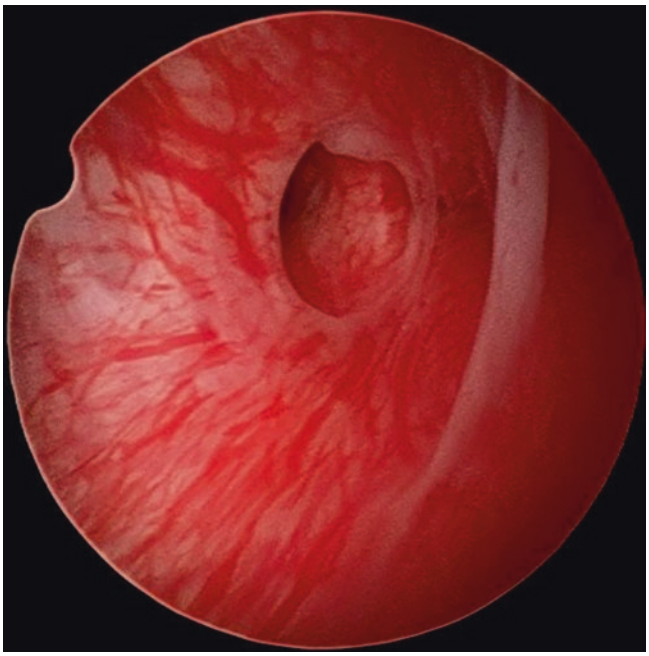

Fig. 9.1 Irregular endometrium with small defects seen on the endometrial surface. Appreciate a magnification of a small defect

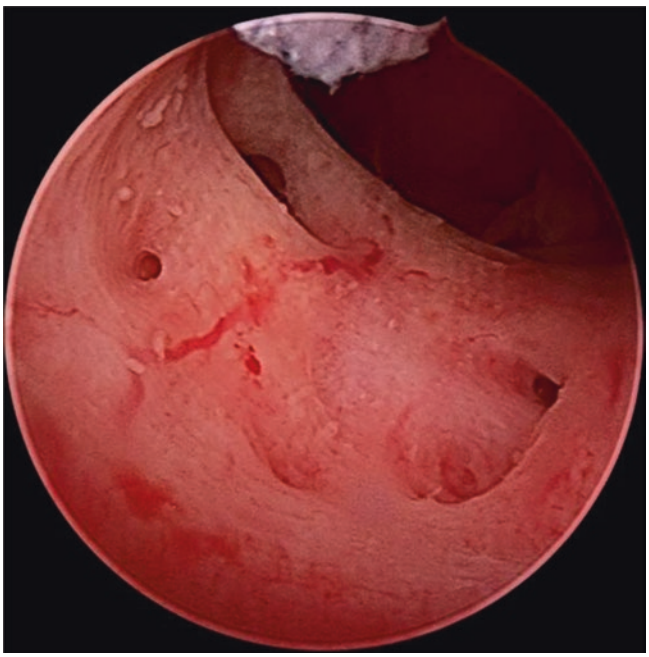

Fig. 9.2 Defects on the endometrial surface with some strawberry pattern

4. Fibrocystic appearance of intrauterine lesions (Fig. 9.8)
5. Hemorrhagic cystic lesions with dark blue or chocolate brown appearance (see Figs. 9.9, 9.10, and 9.11)

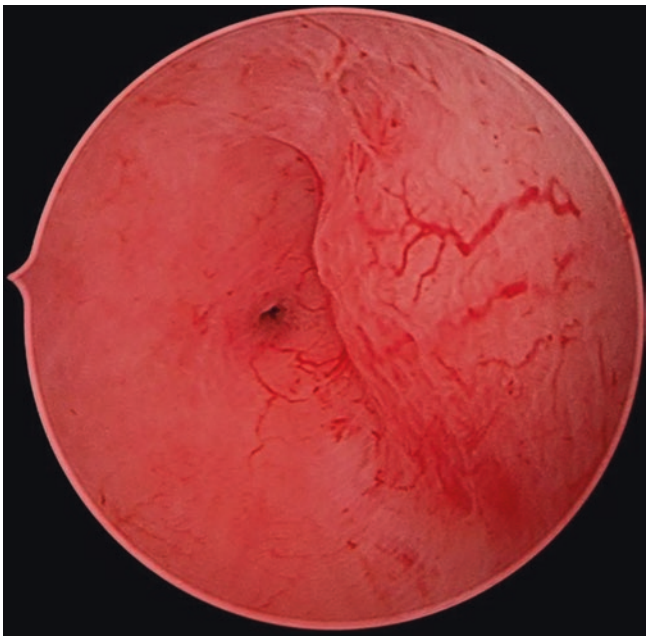

Fig. 9.3 Irregular endometrial surface

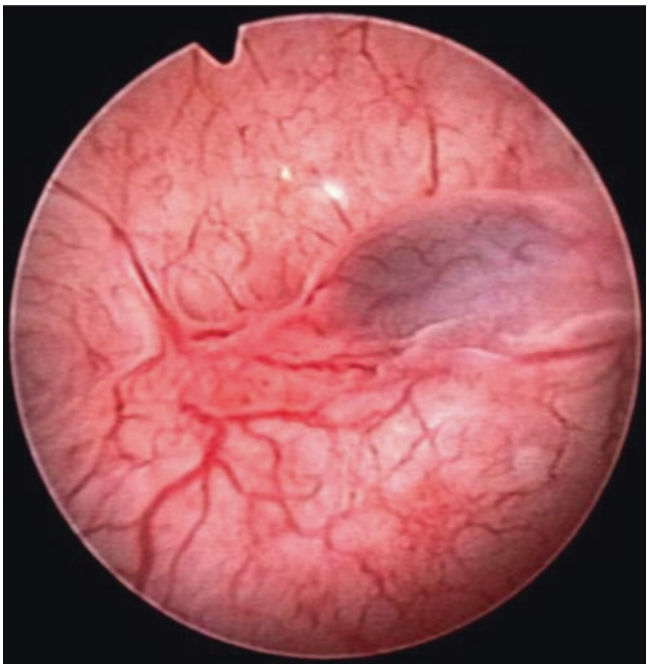

Fig. 9.5 Cystic adenomyosis. Appreciate the purple color due to blood collection

Fig. 9.4 Pronounced bulge in endometrial cavity with altered vascularization

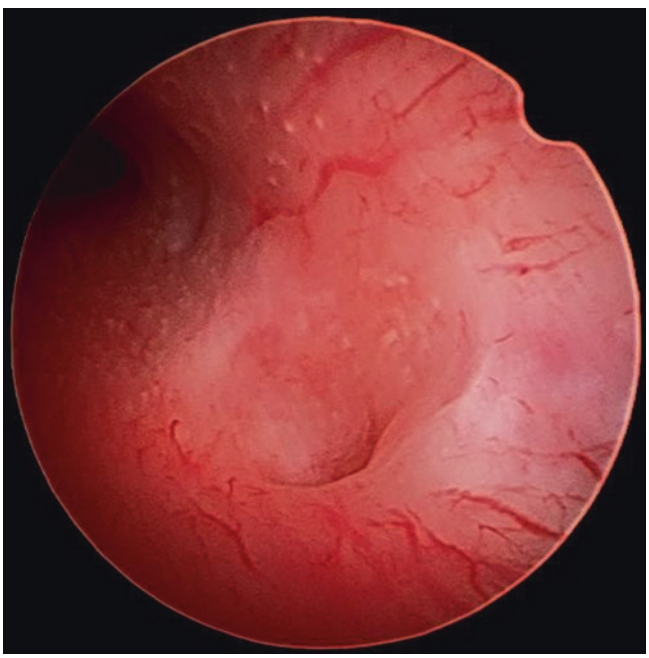

Fig. 9.6 The pathognomonic hysteroscopic signs and visible clues of adenomyosis include (1) bulge in endometrial cavity, (2) an irregular endometrium with endometrial defects, (3) altered vascularization, and (4) cystic hemorrhagic/bluish lesion

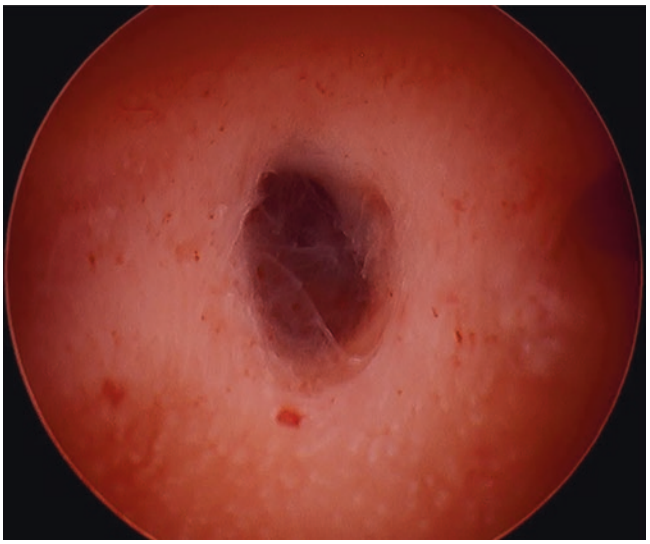

Fig. 9.7 Appreciate the evident strawberry pattern and irregular superficial endometrium

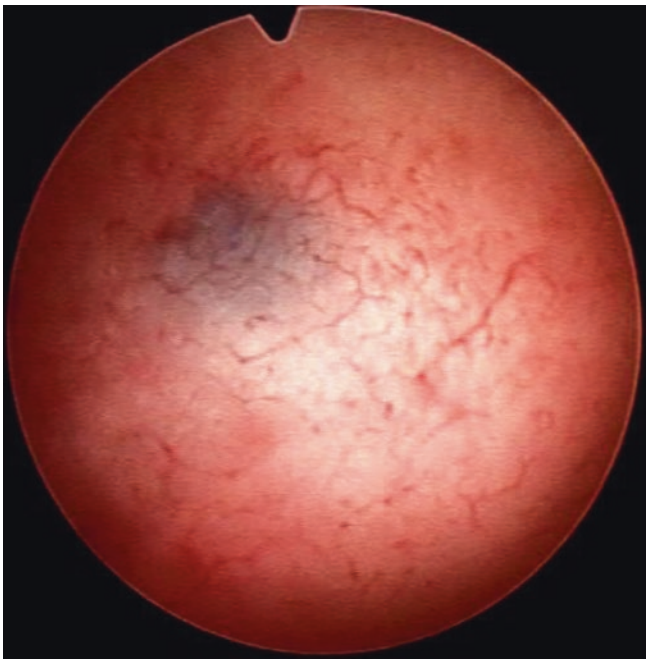

Fig. 9.9 Irregular endometrium with endometrial defects. (3) Altered vascularization and purple endometrial lesion

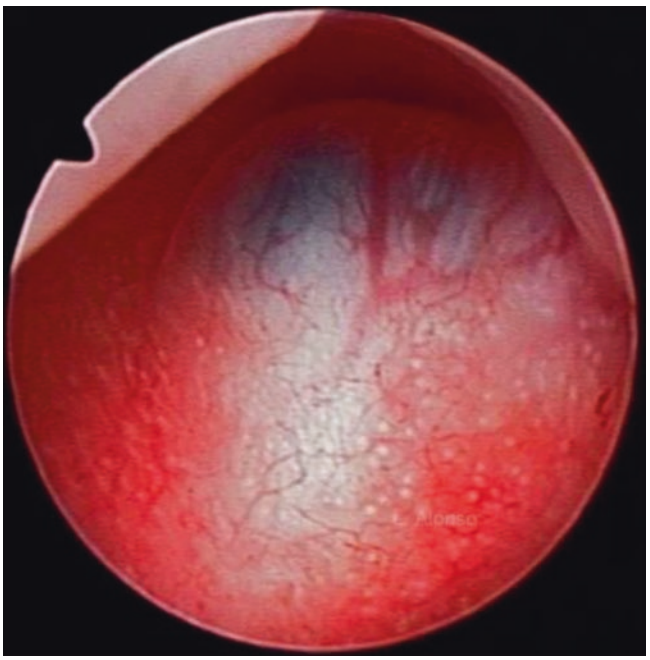

Fig. 9.8 Appreciate a detailed magnification of cystic adenomyosis

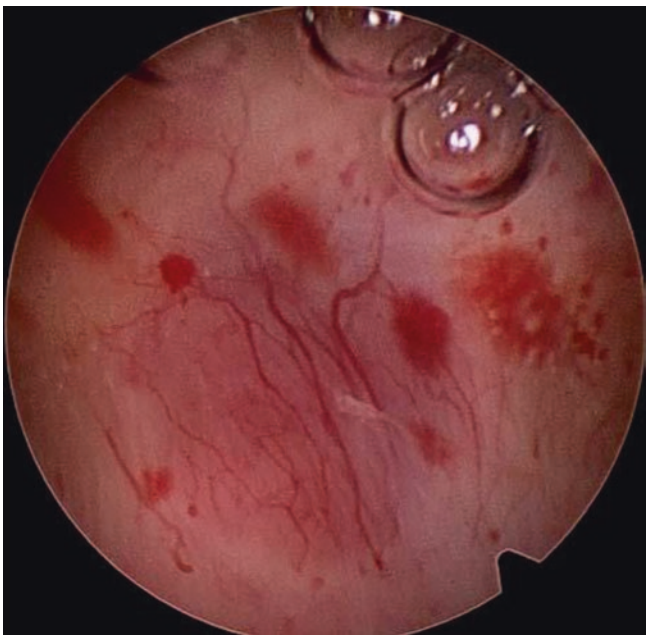

Fig. 9.10 Hysteroscopic view of irregular endometrial pattern characteristic of endometriosis/adenomyosis

Fig. 9.11 Small purple spot and strawberry endometrial pattern.

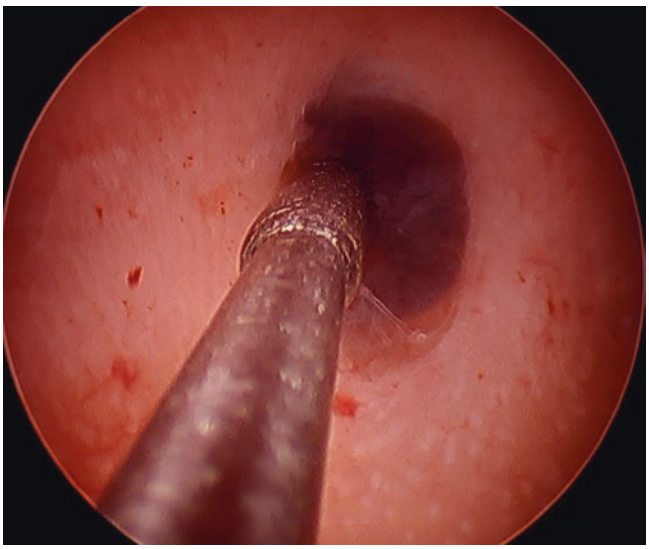

Fig. 9.12 Use of hysteroscopic scissors to drain cystic adenomyosis implants

9.5 Management

Hysterectomy is the treatment of choice for symptomatic women who have completed childbearing. For women with adenomyosis who desire future pregnancy, hormonal medications may provide temporary symptomatic relief. Hysteroscopy, although not considered first-line treatment of adenomyosis, also represents a viable option in selected cases of focal or superficial type. The use of both mechanical instruments, such as hysteroscopic scissors, and bipolar electrode to excise small adenomyotic implants as well as the use of the resectoscope for larger lesions have been previously described which depict the sequence of the opening of cystic adenomyoma using hysteroscopic scissors [22, 23] (Figs. 9.12, 9.13, and 9.14).

In cases of deep, diffuse adenomyosis, however, studies have shown that hysteroscopy is not an appropriate treatment option, as other surgical treatments including hysterectomy are recommended [24].

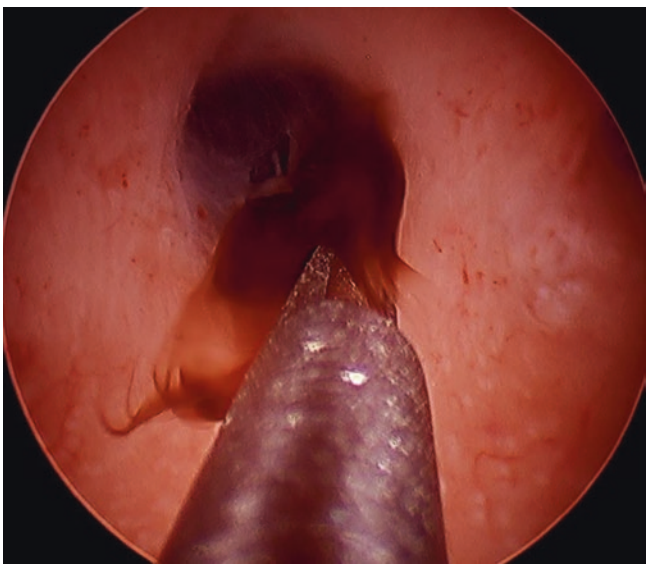

Fig. 9.13 Appreciate blood extravasation after incision of adenomyosis cystic implant

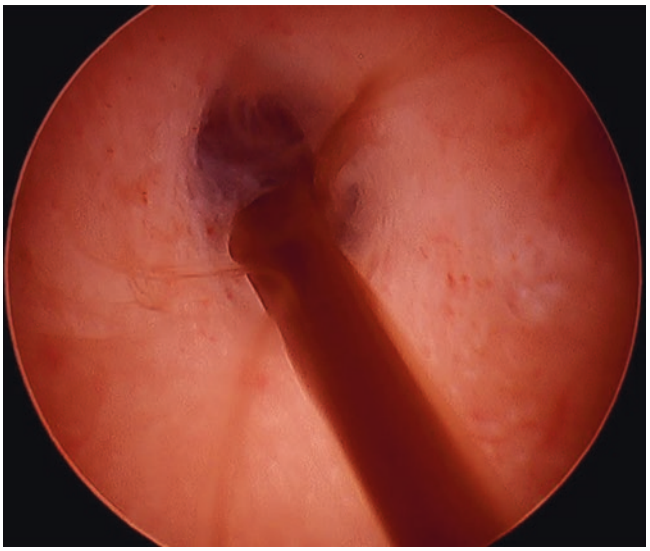

Fig. 9.14 Active blood extravasation of adenomyosis after surgical hysteroscopic incision

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Isthmocele

10

Mario Franchini, Paolo Casadio, Pasquale Florio, and Giampietro Gubbini

Interest in the potential clinical relevance of isthmocele, cesarean scar defect (CSD), pouch, or niche has increased in the last years (Figs. 10.1 and 10.2).

Isthmocele is commonly detected as an incidental finding on transvaginal ultrasound (TVS) as a wedge-shape anechoic area at the site of previous cesarean section (CS) [1].

Isthmocele is usually asymptomatic or relates to postmenstrual spotting and dark red or brown discharge, pelvic pain, or infertility [2].

With the increasing CS rate worldwide, the prevalence of an isthmocele in a random population ranged from 24% to 70% and from 56% to 84% when assessed by TVS and contrast infusion sonography, respectively (HyCoSy) [3]. Furthermore, the prevalence by TVS examination is higher (70–84%) in women with symptoms and was similar between groups of women examined at 3–12 months, 1–5 years, or 5–10 years after CS [4, 5]. Recently, HyCoSy, using saline or gel, has been considered the method of choice for detecting isthmocele especially when fluid is not present naturally in the pouch [6, 7].

In 2016, a practical guideline for examining a uterine niche using ultrasonography in nonpregnant women has been proposed by European experts [8]. Finally, the reliability of volume estimation and morphologic assessment of isthmocele might improve with three-dimensional saline contrast sonohysterography (3D-SCSH) supported by SonoHysteroAVC or VOCAL, but the relevance in clinical practice is still under evaluation [9].

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The treatment of isthmocele is performed to relieve symptoms (postmenstrual spotting, suprapubic pelvic pain, dysmenorrhea, dyspareunia, and infertility), and consequently the asymptomatic cases should not be treated.

Multiple techniques have been used for CSD treatment: reconstructive therapies including laparoscopic or robot-assisted laparoscopic excision, vaginal repair, and channel-like resectoscopic treatment. All these procedures excise or ablate the fibrotic tissue of niche, suggesting that the removal of the local inflamed tissue may contribute to the improvement of symptoms [10].

Hysteroscopic treatment is performed, after the bladder is filled with methylene blue solution, with small variations among surgeons, by resecting, with monopolar or bipolar loop, the fibrotic tissue of the inferior/distal rim of the niche (closest to the external cervical os) (Fig. 10.3a) proposed by Fabres [11–15] or with superior/proximal edge of the defect (closest to the uterine cavity) (Fig. 10.3b) proposed by Gubbini [16–18]. The procedure is ended, using a rollerball or loop electrode, with coagulation of fragile vessels of niche celling [11, 12] (Figs. 10.4 and 10.5) or superficial coagulation of entire isthmocele surface [13, 14, 16, 19] or with 360-degree resection (endocervical ablation) of the all residual cervical canal inflamed tissue surrounding the diverticulum [16, 18].

Isthmoplasty is usually performed using a 26Fr or 27Fr resectoscope after cervical dilation. Recently, a 16Fr or 15Fr resectoscope has been used for resectoscopic CSD treatment with the advantages of vaginoscopic approach and without the complications related to cervical dilation [20] (Fig. 10.6).

The 15–16Fr resectoscope allows the surgeon to perform standard maneuvers of 26–27Fr resectoscopic treatment with miniaturized instrumentation [20] (Fig. 10.7).

Channel-like resectoscopic treatment restores the continuity of the cervical canal, and improves, flattening the isthmocele area, menstrual drainage reducing blood accumulation in the pouch and reflux into the uterine cavity [12–15]. Finally, isthmoplasty reduces, with superficial coagulation,

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_10

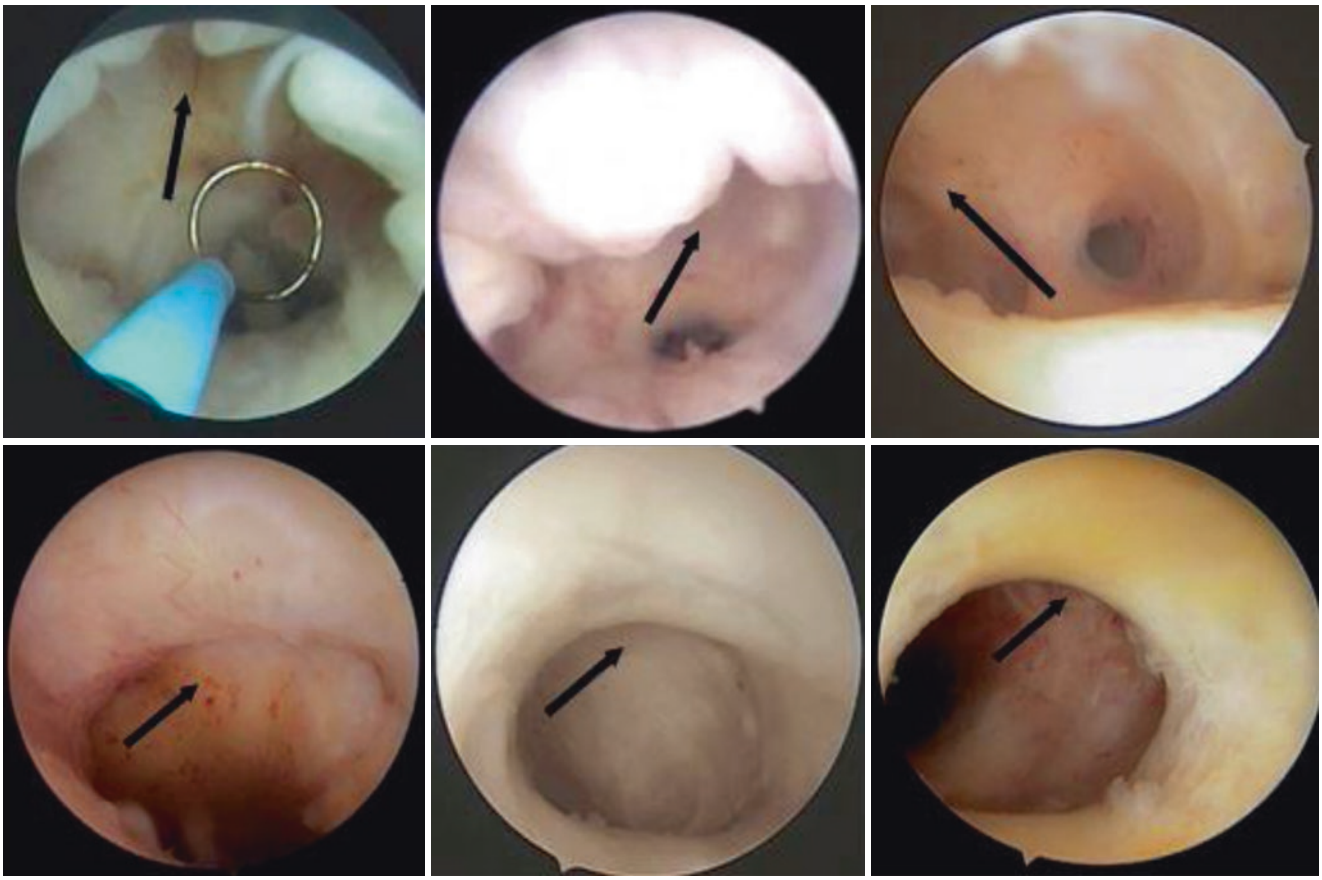

Fig. 10.1 Hysteroscopic appearance of isthmocele (black arrows)

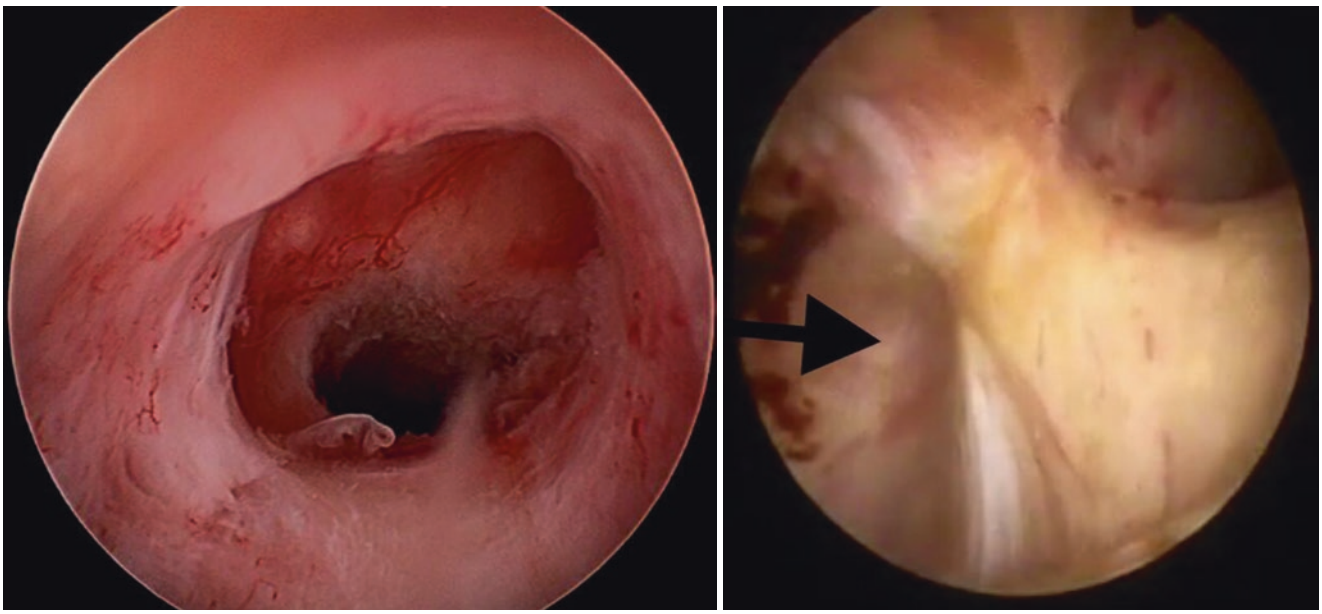

Fig. 10.2 Hysteroscopic appearance of isthmocele

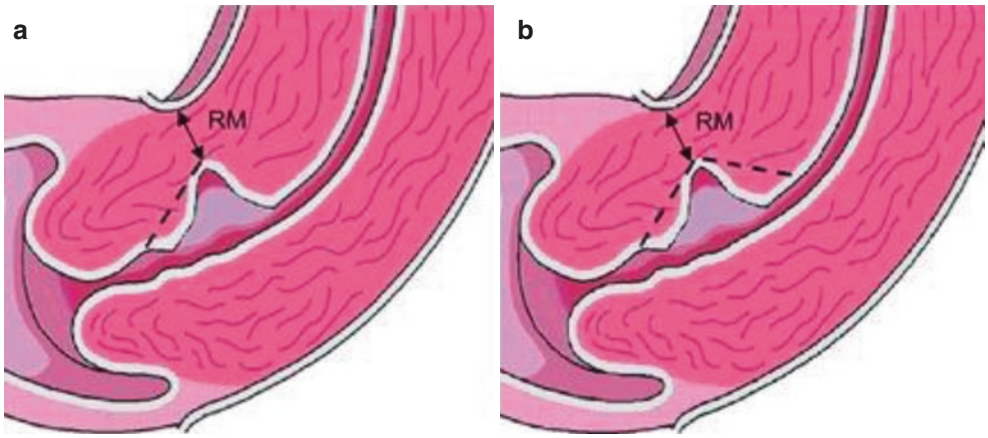

Fig. 10.3 Hysteroscopic isthmocele treatment is performed by resecting only (**a**) the inferior/distal rim of the niche (Fabres, 2005) or (**b**) removing the fibrotic tissue of the inferior/distal and superior/proximal of the defect (Gubbini, 2008). Residual myometrium (RM)

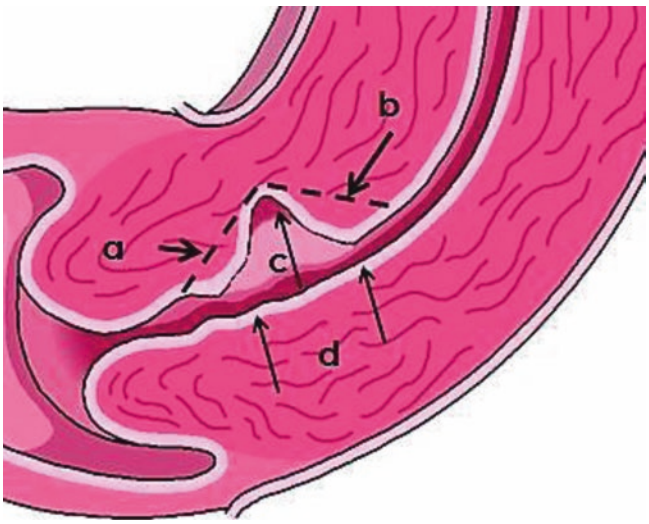

Fig. 10.4 Isthmoplasty: channel-like resectoscopic treatment of CSD. (**a**) Resection of the fibrotic tissue of the proximal part. (**b**) Resection of the fibrotic tissue of the distal part. (**c**) Coagulation of niche surface with a rollerball electrode. (**d**) 360-degree "endocervical ablation" surrounding the diverticulum. Figure modified from Gubbini et al. [12]

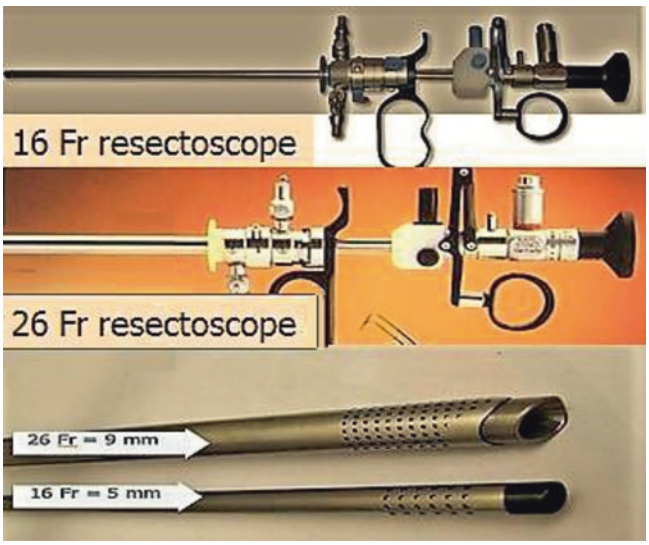

Fig. 10.6 Continuous-flow operative resectoscope. Size comparison between the 16 Fr (Gubbini system, Tontarra, Medizintechnik, GmbH, Germany) and 26 Fr resectoscope (Karl Storz, Tuttlingen, Germany)

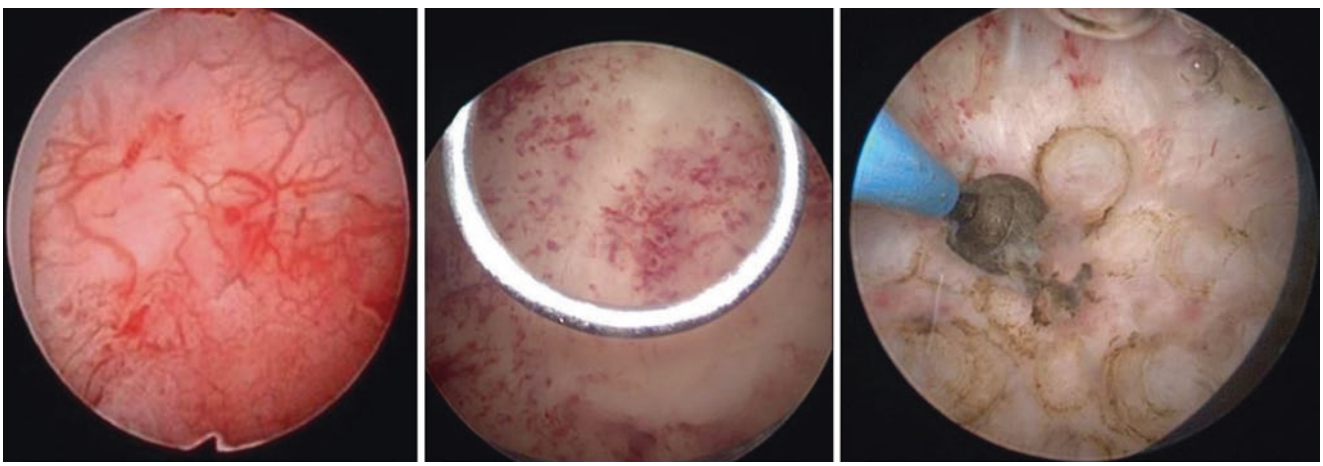

Fig. 10.5 Fragile vessels of isthmocele celling: superficial coagulation, using a rollerball or loop electrode

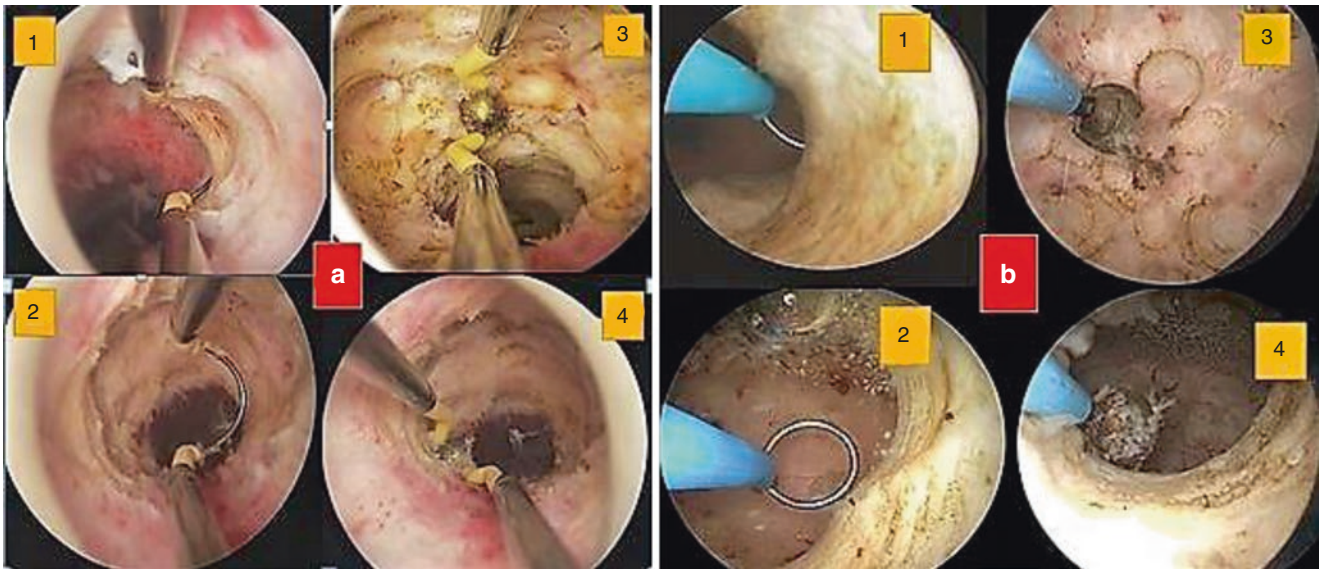

Fig. 10.7 Surgical technique for isthmoplasty. (**a**) 26 Fr resectoscope and (**b**) 16 Fr resectoscope. (1, 2) Resection of the fibrotic tissue of the distal and proximal part of the niche. (3) Coagulation of the entire niche surface superficially with a rollerball electrode. (4) 360-degree "endocervical ablation" of the all-residual cervical canal inflamed tissue surrounding the diverticulum

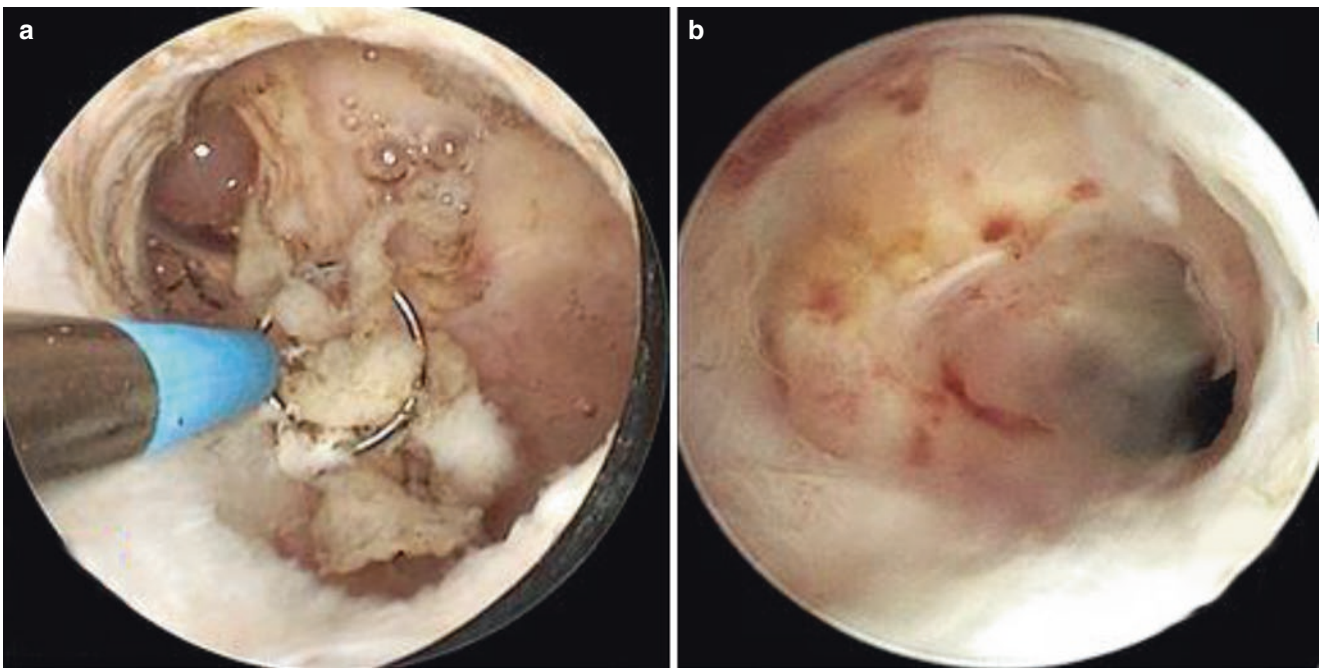

Fig. 10.8 Hysteroscopic isthmocele appearance (**a**) during resection of fibrotic tissue and (**b**) after 6-month follow-up

blood loss from fragile vessels of niche surface and replaces, with endocervical ablation, inflamed tissue surrounding the diverticulum, with mono stratified cubic cell-type epithelium [16, 18] (Fig. 10.8).

After hysteroscopic approach, a significant postoperative improvement of uterine bleeding was observed in 59–100% of cases [1, 2] and more frequently in patients with anteflexed uteri than in patients with retroflexed uteri [14].

Since the isthmocele may impair fertility, because of the persistence and accumulation of the menstrual blood in the cervix (Fig. 10.9), creating a toxic environment around the scar [21, 22], hysteroscopic removal of the local inflamed tissue contributes to the improvement of fertility with a pregnancy rate of 77.8–100% [23–25].

Hysteroscopic isthmoplasty appears to be the most popular approach for the treatment of isthmocele. There is a

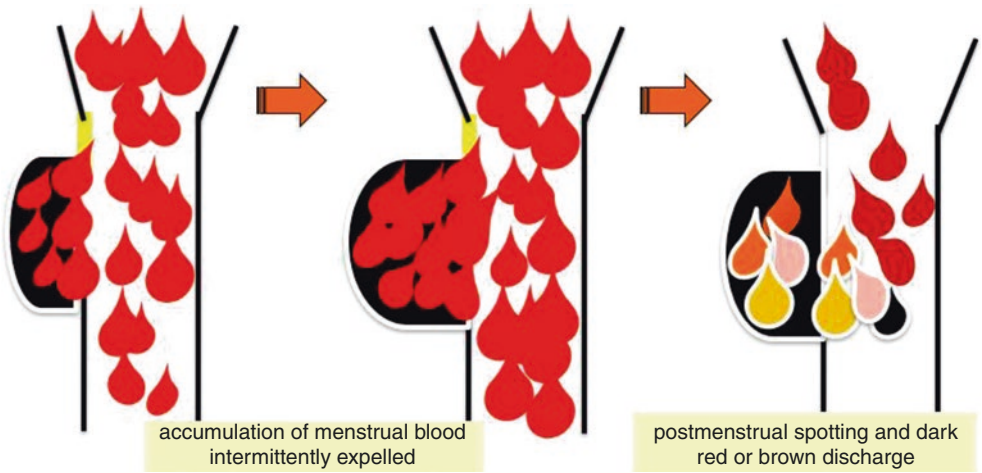

Fig. 10.9 Persistence and accumulation of the menstrual blood in isthmocele

trending opinion that CSD could be associated with a risk of uterine perforation and bladder injury when residual myometrial thickness (RMT) is less than 2–3 mm [12, 26, 27]. However, to the best of our knowledge no single case of uterine wall perforation and bladder injury has been reported yet independently from the size of RMT [28].

Nevertheless, complications result to be lower after channel-like resectoscopic treatment than by vaginal or laparoscopic approach [25]. Moreover, the hysteroscopic CSD repair time is considerably reduced 11–23 min [23] when compared to laparoscopic 42–117 min [29, 30], robotic 240 min [31], or vaginal approach 33–120 min [32, 33].

In conclusion, a widely accepted approach for the treatment of cesarean scar defects has not been yet developed. In the absence of randomized trials evaluating the efficacy of different surgical approaches, hysteroscopic isthmoplasty appears to be the most popular and less invasive after shared decision-making has been evaluated with the patient.

Acknowledgment *Disclosure statement*: The author Giampietro Gubbini is the inventor of "Gubbini system," hence no royalties.

The authors Mario Franchini, Paolo Casadio, and Pasquale Florio have nothing to disclose.

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Infections and Inflammations

11

Ettore Cicinelli and Alka Kumar

11.1 Introduction

In the last years a growing scientific interest has been focused on chronic endometritis and on the consequences of this pathology on reproduction [1].

Chronic endometritis (CE) is the chronic or subacute inflammation of the endometrial mucosa. Inflammation of the endometrial mucosa may be caused by noninfectious factors and hormonal and immunological disorders but in most of cases it is thought that CE is due to an underlying infection of the uterine cavity [2, 3].

The traditional concept of a sterile uterine cavity has been recently confuted and now we know that uterine cavity harbors a specific microbial flora. Notably, due to the characteristics of the bacteria the routine microbial culture of the endometrium is often negative but today it is possible to examine the entire endometrial microbiome with the use of genomic testing [3–5]. By this technique it has been profiled a specific endometrial microbiota that is highly stable and dominated by Lactobacilli. Any changes in microbiota profile appear to be associated with adverse reproductive outcomes [3–5].

Special reference needs to be made to the role of tuberculosis. In many countries over the world and also in industrialized countries tubercular bacillus is a frequent cause of chronic endometritis which shows some specific features [6]. Endometrial tuberculosis tends to manifest as infertility and/or lower abdominal pain. Endometrial tuberculosis may have severe reproductive consequences on fertility in spontaneous as well as in vitro fertilization cycles [7].

Diagnosis of CE is challenging. Clinically, the presence of CE is frequently overlooked as this pathology is poorly known by many specialists and because it lacks specific symptoms. In fact, in many cases CE is asymptomatic, or it may cause abnormal uterine bleeding, pain, infertility, and covert ART failures.

Due to its ceiled nature the reported incidence of CE in women with reproductive problems shows a great variability ranging from 30% to 60% of patients with repeated implantation failure in ART [8–10] and 50% to 60% of women with recurrent pregnancy losses (RPL) [11, 12] to only 2% among women prior to their first IVF cycle [13].

This wide variability in the incidence of CE is also explained by the lack of standardized and reproducible diagnostic criteria for this pathology. Histology is considered the gold standard for diagnosing CE based on plasma cell detection [2] but it remains an operator-dependent technique. Recently, CD138 immunohistochemistry staining for plasma cells has provided higher diagnostic accuracy, sensitivity, and reduced intra- and inter-observer variability as compared to hematoxylin and eosin (H&E) analysis [12, 14]. However, even about interpretation of CD138 immunohistochemistry staining no consensus exists. Different criteria have been reported in the literature regarding the number and distribution of plasma cells needed for diagnosis [13].

Fluid hysteroscopy is a reliable technique for diagnosing CE. Saline infusion provides a smooth distention of the uterine cavity, no compression of small surface lesions, and floating of any intraluminal lesions. In this way it is possible to perform a very accurate exploration of the endometrial surface [2, 15, 16] and to detect even small lesions that are characteristic for this pathology. However, at the moment even by the majority of hysteroscopists the diagnosis of CE is often missed. In fact, need of knowledge and skill, high inter-observer variability, and not still defined diagnostic

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_11

criteria make the hysteroscopic diagnosis of CE difficult and frequently missed.

In this chapter we try to describe the most important hysteroscopic aspects related to CE.

11.1.1 Technique

Hysteroscopy may be performed using vaginoscopic approach or using vaginal speculum. In our personal experience in women seeking for a pregnancy we prefer to apply the speculum in order to minimize the contact of the endoscope with vaginal content and the transport of infectious agents into the uterine cavity.

The use of thin endoscopes (less than 4 mm) is advised as these patients due to inflammatory status of the uterus are at risk of feeling more pain compared to other women. We use lens-based mini-hysteroscopes (2.7 mm OD mini-telescope), equipped with a 3.5 mm OD single-flow diagnostic sheath. The hysteroscopies should be performed preferentially in the follicular phase.

Saline but not CO_2 should be employed to distend the uterine cavity. Saline should be employed at a pressure of about 50–60 mmHg generated by dedicated electronic pumps or by simple drop from a bag suspended 1 m above the patient. Compared to gas, the employment of saline provides a smoother distention of the uterine cavity, avoids the effects of CO_2 on endometrial microcirculation, and allows the continuous washing of the uterine cavity and mainly the floating of even minimal endometrial ingrowths (notably, the CO_2 causes the flattening of small structures against the endometrial surface so that they cannot be detected).

As usual appropriate light sources, digital cameras and video recording facilities are required.

During hysteroscopy both the anterior and posterior uterine walls must be thoroughly examined by approaching the hysteroscope along the endometrial surface in order to get a view parallel to the endometrial surface. In this way, any irregularity of the endometrial surface may be easily identified (Figs. 11.1, 11.2, and 11.3).

All procedures should be performed without any kind of anesthesia.

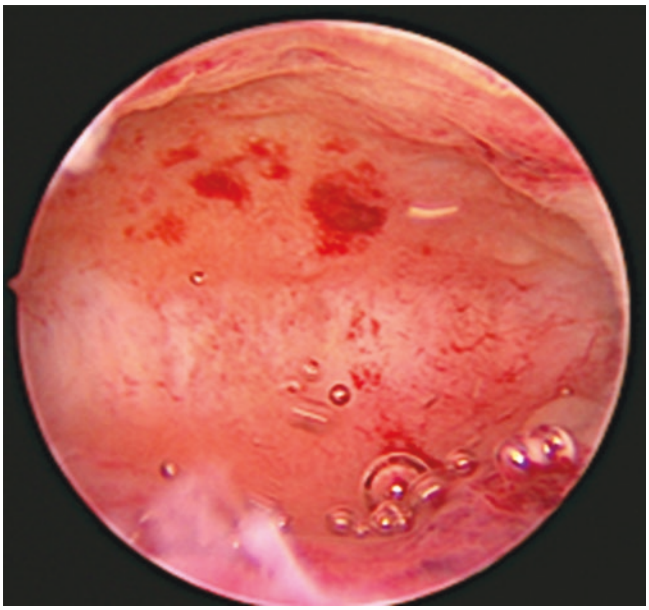

Fig. 11.1 Focal endometrial hyperemia: the endometrium shows foci and spots of hyperemia in the fundal area and in the anterior wall

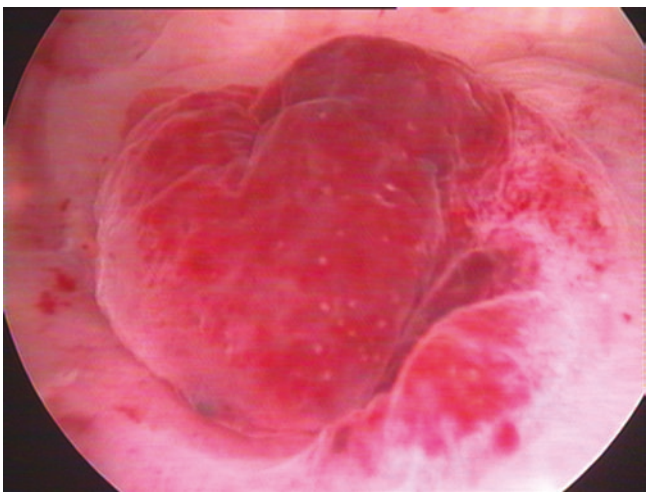

Fig. 11.2 Hyperemic polyp and multiple spots of redness: the endometrium shows a dishomogenous thickness

11.1.2 Main Hysteroscopic Features for CE at Fluid Hysteroscopy

(a) Micropolyps: These are pedunculated translucent structures less than 1 mm in size (Figs. 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, and 11.10). They occur as sporadic isolated structures or occur in clusters. The micropolyps occur anywhere inside the uterine cavity and are generally diffuse in nature and distribution.

(b) Whitish and tick endometrium (stromal edema is a histological and not hysteroscopic diagnosis): The endometrium may appear whitish and irregularly thick due to increased stromal edema (Figs. 11.6, 11.8, 11.9, and 11.10). The underlying vascularity cannot be viewed anymore. The stromal edema may be localized or diffused to all the cavity. The stromal edema can be identified only when the endometrium is viewed parallel and along the long length the endometrium and cannot be appreciated in any other orientation.

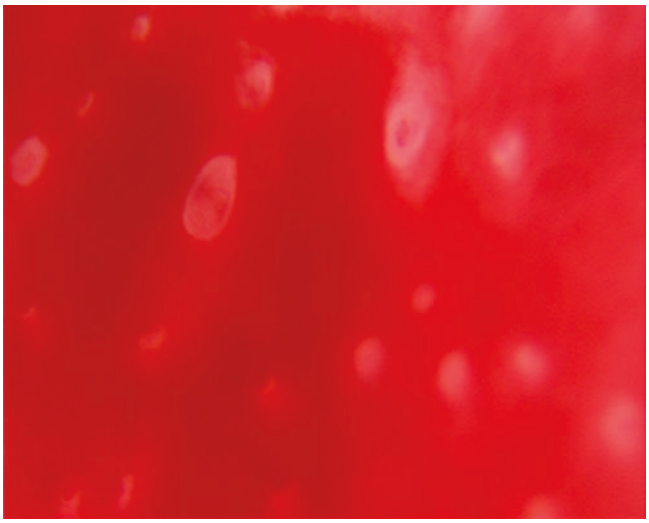

Fig. 11.3 Strawberry appearance and hyperemia at close observation: the endometrium shows hyperemia of a diffuse nature. The endometrial gland openings appear intense whitish and surrounded by intense hyperemia, thereby giving a strawberry-like appearance. However, on close observation it can be observed that each endometrial gland has its own independent and separate rounded zone of hyperemia which differentiates it from the early proliferative endometrium and endometrium redness of an insidious nature

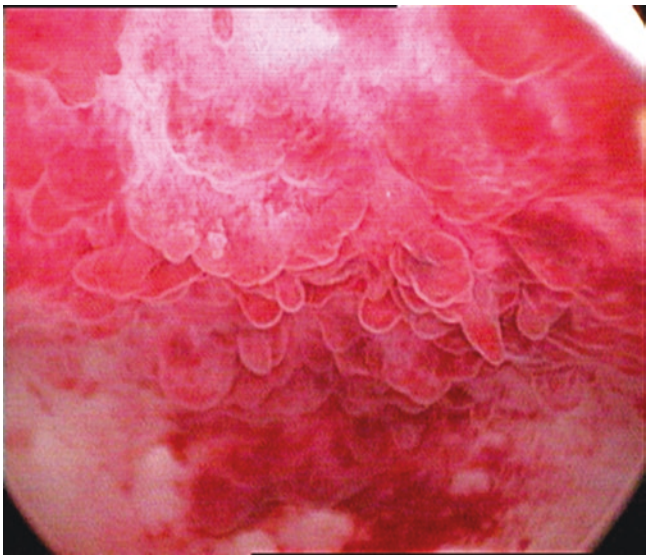

Fig. 11.4 Focal hyperemia and micropolyps: in this case redness of the endometrial mucosa is associated to the presence of micropolyps which are pedunculated translucent structures less than 1 mm in size. They occur as sporadic isolated structures or occur in clusters

(c) Undulating or pseudopolypoid endometrium: The endometrium surface is rough and undulating showing mucosal folds that resemble polyps (Figs. 11.9, 11.10, 11.11, and 11.12). The undulating nature of the endometrium is best appreciated with the hysteroscope making an angle of about 45° with the endometrium.

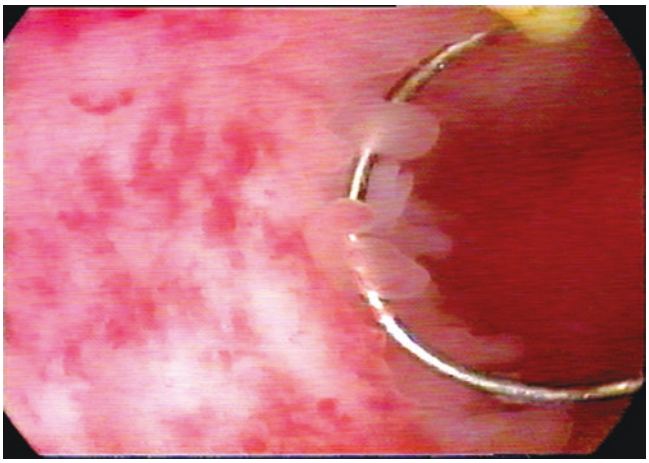

Fig. 11.5 The cutting loop of the resectoscope is lifting some micropolyps

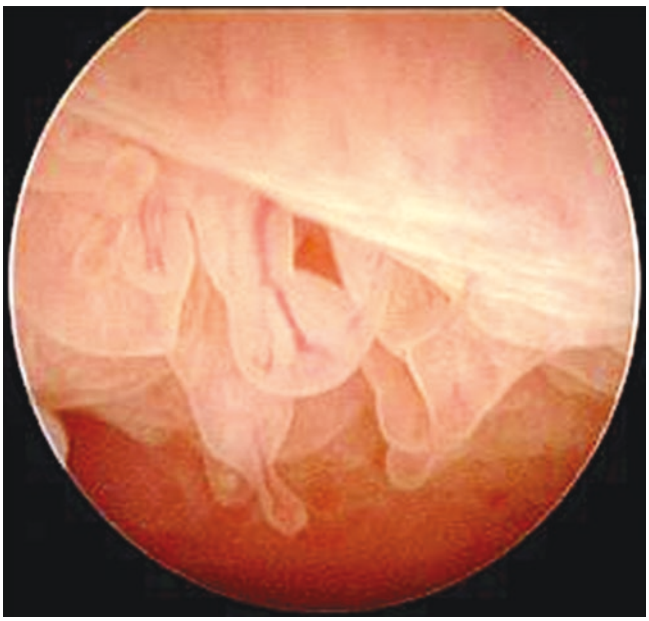

Fig. 11.6 Diffuse micropolyps on the anterior endometrial wall. Micropolyps appears as pedunculated translucent structures less than 1 mm in size with a visible vascular axis

(d) Strawberry appearance and hyperemia: The endometrium shows either patches of hyperemia or hyperemia of a diffuse nature [1–4, 7, 9]. The endometrial gland openings appear to be intense whitish and surrounded by intense hyperemia, thereby giving a strawberry-like appearance. However, on close observation it can be observed that each endometrial gland has its own independent and separate rounded zone of hyperemia which differentiates it from the early proliferative endometrium and endometrium redness of an insidious nature.

(e) Tuberculosis of the endometrial cavity: Many past studies have considered fluid hysteroscopy to be a reli-

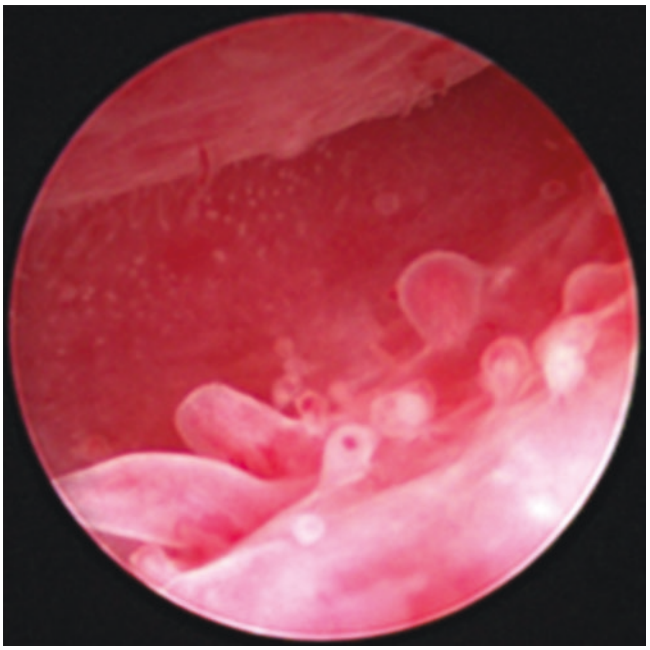

Fig. 11.7 Diffuse micropolyps combined with diffuse redness of the endometrial surface

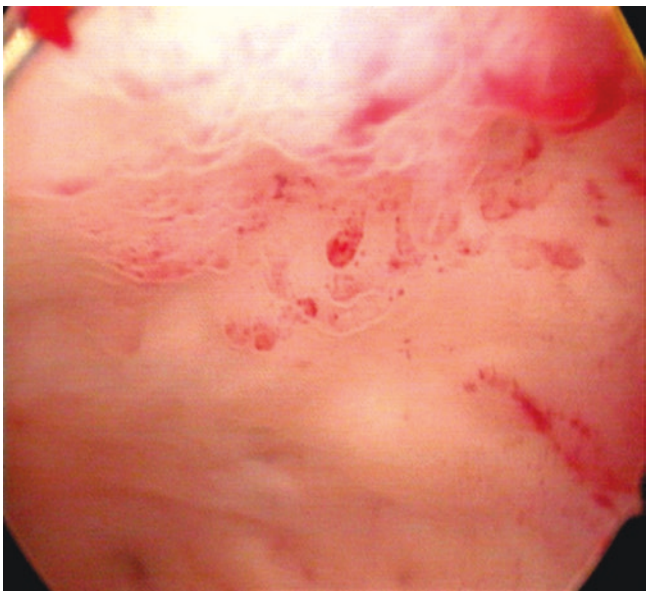

Fig. 11.8 Whitish and tick endometrium (stromal edema is a histological and not hysteroscopic diagnosis) in the follicular phase. The endometrium may appear whitish and irregularly thick due to increased stromal edema mimicking a secretory phase. The presence of micropolyps and small areas of redness may help in the diagnosis of CE

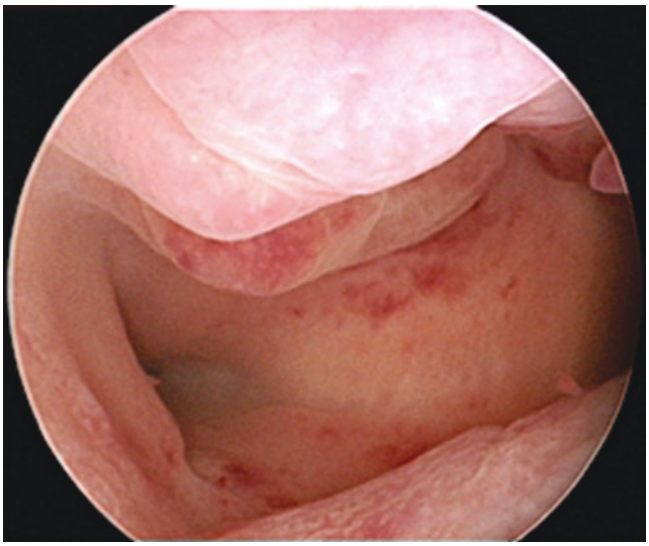

Fig. 11.9 Whitish and tick endometrium with the characteristics of secretory phase. The endometrium appears whitish and irregularly thick with a pseudopolypoid aspect. The presence of sparse micropolyps and areas of redness may suggest the diagnosis of CE

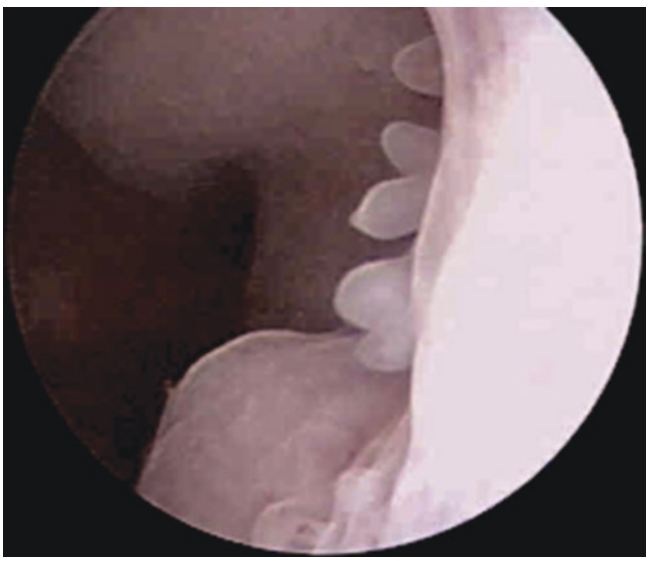

Fig. 11.10 Whitish and tick endometrium with the characteristics of secretory phase. The endometrium appears whitish and irregularly thick with a pseudopolypoid aspect. The presence of a cluster of micropolyps may suggest the diagnosis of CE

able and useful examination for investigating endometrial tuberculosis [6, 7, 16–19]. Hysteroscopy is a useful modality in diagnosing endometrial tuberculosis. Classical hysteroscopic finding of endometrial tuberculosis is a rough dirty-looking bizarre pale endometrium with gland openings not seen and with overlying whitish deposits [6, 7] and adhesions (Fig. 11.13a, b). However, all these signs may not be seen in the same case or their intensity may vary. In order to reach to a diagnosis, the markers of tuberculosis must be carefully evaluated. Whitish deposits are the most pathognomonic of tuberculosis; however they may not always be seen especially since the superficial layer of the endometrium sheds every 28 days and along with the endometrium the said deposits also shed [20]. Hence

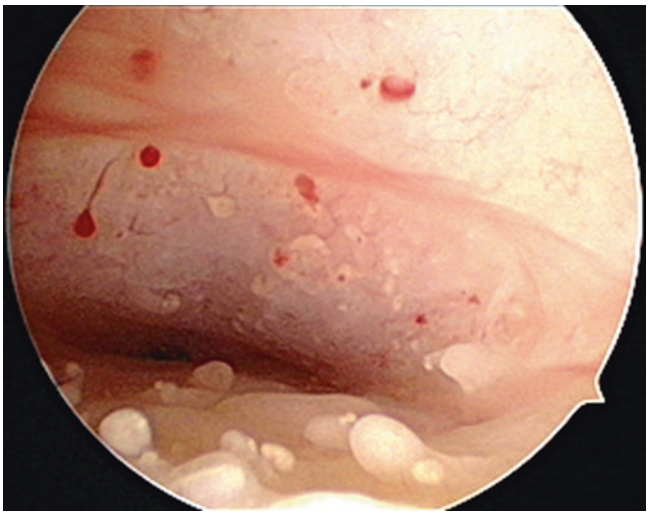

Fig. 11.11 Whitish and tick endometrium with the characteristics of secretory phase. The endometrium appears whitish and irregularly thick with a pseudopolypoid aspect. The presence of diffuse micropolyps and spots of redness may suggest the diagnosis of CE

Fig. 11.12 Undulating or pseudopolypoid endometrium in combination with micropolyps, diffuse and focal hyperemia. The endometrium surface is rough and undulating showing mucosal folds that resemble polyps. The endometrial appearance may be suggestive of the combination of endometrial hyperplasia with inflammation. The undulating nature of the endometrium is best appreciated with the hysteroscope making an angle of about 45 degrees with the endometrium

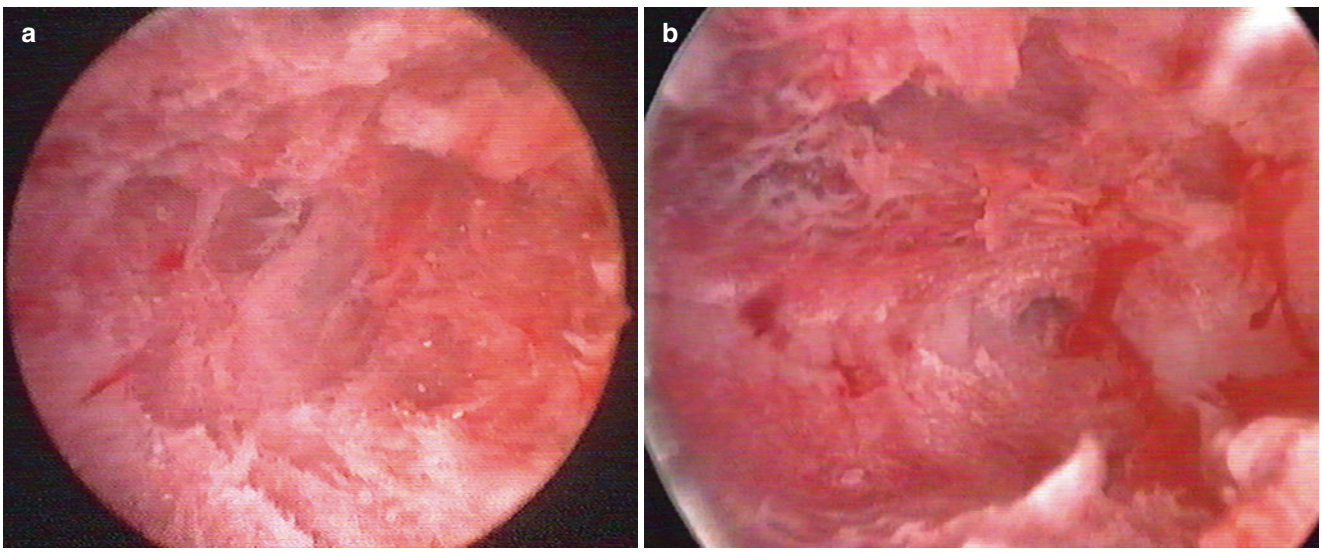

Fig. 11.13 (**a**) A bizarre endometrial architecture. (**b**) A bizarre pale scarred thin dirty-looking endometrium with whitish deposits and flimsy adhesions, and with no endometrial gland openings visible

the best time for conducting hysteroscopic examination is in the premenstrual phase so that any overlying deposits are not missed out. A classical endometrial deposit under high magnification is seen in Figs. 11.14a, b and 11.15. Large tubercles are also often seen (Fig. 11.16). Diagnosis of endometrial tuberculosis is confirmed with PCR and culture of the suspected endometrial tissue. Endometrial scarring is one of the pathognomonic features in endometrial tuberculosis especially if whitish deposits overlying the endome-

Fig. 11.14 Tubercular endometritis: the view is suboptimal due to the abundant intrauterine content and difficulty is washing the cavity. The endometrial mucosa appeared congested and loosely bleeding. Multiple white-colored areas with calcified nodules and irregular whitish deposits can be detected at hysteroscopy

Fig. 11.15 An endometrial tubercular deposit seen under high magnification

trium are also seen. Endocervical scarring is also frequently seen in endometrial tuberculosis. In endometrial tuberculosis intraluminal adhesions in the interstitial part of the fallopian tube can often be viewed at hysteroscopy by placing the microhysteroscope tip very close to the tubal orifice and viewing with a source magnification of 25× [21]. At times the whitish deposits do not overlie the endometrium and instead they are anchored to flimsy adhesions by being impregnated in the same (Fig. 11.17a, b). These flimsy adhesions are not shed with menstruation; hence the impregnated deposits are seen even in the postmenstrual phase. In some cases, the whitish deposits are not seen over the endometrium at hysteroscopy. Such deposits are seen after vital staining with methylene blue dye. In such cases the hysteroscope is removed and chromopertubation is done with methylene blue dye, followed by reintroduction of the hysteroscope. Glistening-white, highly reflective deposits situated are observed against the background of a dark blue-stained endometrium resembling a "starry sky" appearance [18] (Fig. 11.18). We have observed the starry sky appearance and used it to diagnose endometrial tuberculosis on multiple occasions over a 21-year period. It appears that the methylene blue dye is not taken up by the caseous tubercular deposit but is taken up by the surrounding endometrium. The unstained caseous deposit reflects white light in contrast to the surrounding dark blue endometrium, thereby giving a starry sky appearance. At times panoramic hysteroscopy with 1× magnification using a conventional telescope (27,005 BA; Karl Storz GmbH & Co., Tuttlingen, Germany) reveals an endometrium unremarkable except for subtle scarring, which could also be overlooked. The endometrium is next visualized using a Hamou Micro-Hysteroscope II (26,157 BT; Karl Storz) in the panoramic view at 20× at-source magnification, which reveals a rough-looking endometrium as though it had been sprinkled with a coarse

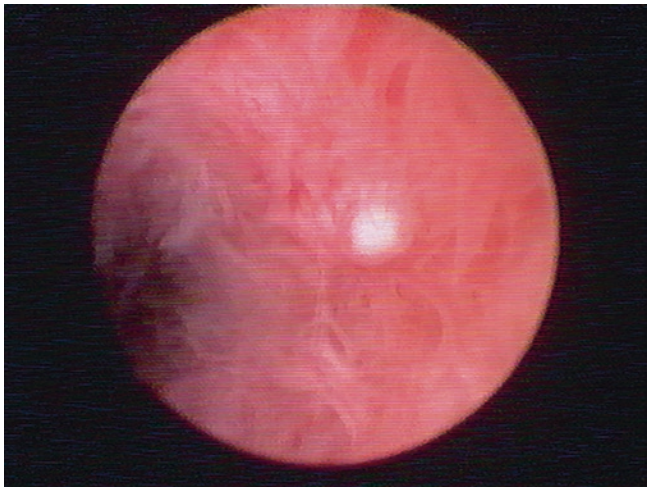

Fig. 11.16 A whitish tubercle is present over the scarred left lateral wall of the endocervical canal

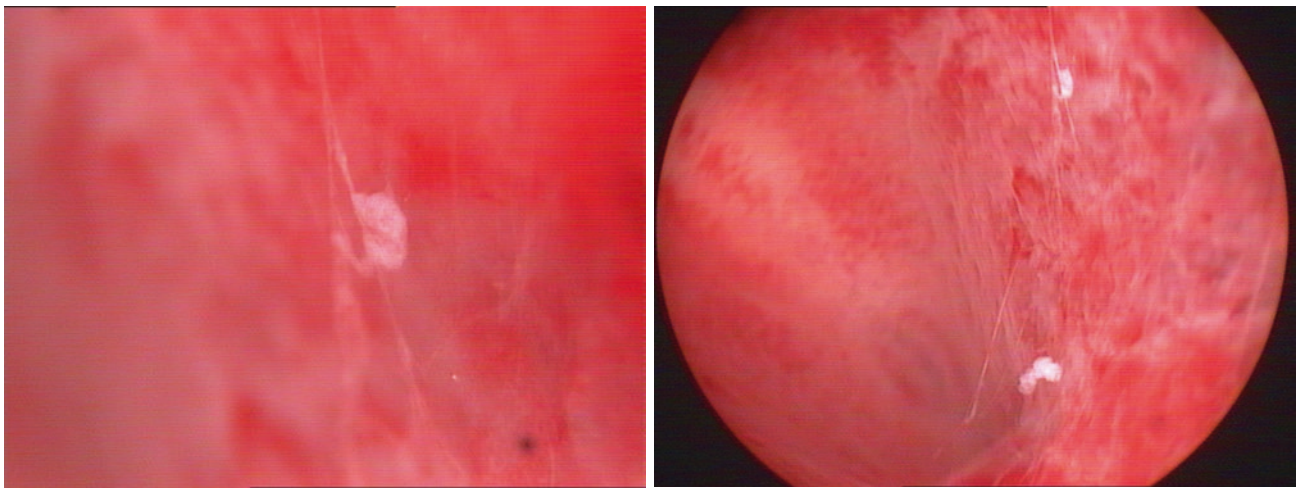

Fig. 11.17 (**a**) Tubercular deposits impregnated over flimsy adhesions. (**b**) Tubercular deposits impregnated over flimsy adhesions

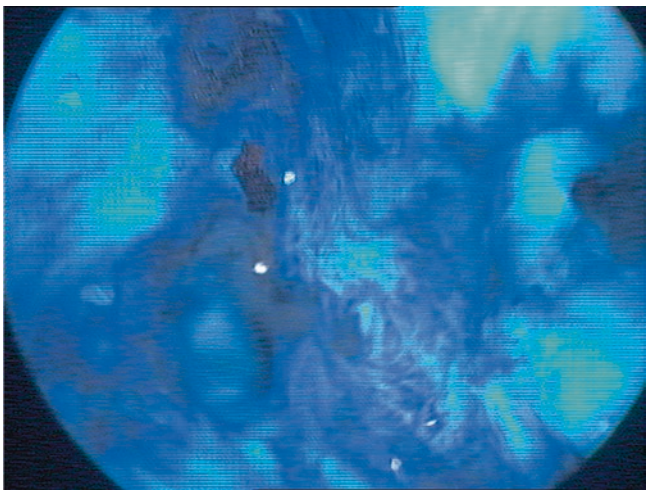

Fig. 11.18 Starry sky appearance over the anterior uterine cavity wall

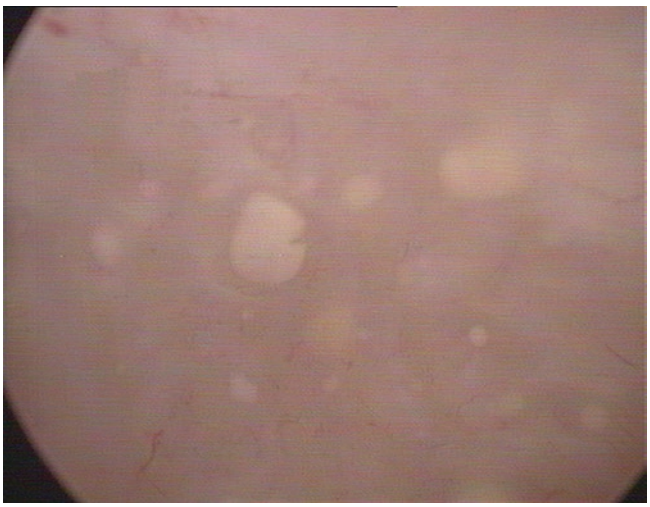

Fig. 11.19 Endometrial tubercular abscess

whitish powder. The endometrial surface is bumpy, with diffusely scattered small conical papillary projections, and no endometrial glands are observed. Herein the term "at-source magnification" relates to the magnification provided by the telescope and not by the video mechanism of the telescope. Hysteroscopic visualization of the endometrium after antitubercular therapy often shows an improvement in the mucosal morphology [7]. A closer visualization at increased magnification is helpful in demonstrating the remnants of a healing tubercular pathology after antitubercular therapy [7]. Relook hysteroscopy after antitubercular therapy guides the surgeon towards prognosis and results of antitubercular therapy (Figs. 11.19, 11.20, and 11.21).

(f) Combination of markers: All the above-described hysteroscopic markers may be present singularly or combined in different ways with other markers.

(g) Differential diagnosis: Thickening and pseudopolypoid aspect of the endometrial mucosa pose a differential diagnosis with endometrial hyperplasia that could coexist with inflammation. In this case, areas of redness and micropolyps are useful markers of inflammation.

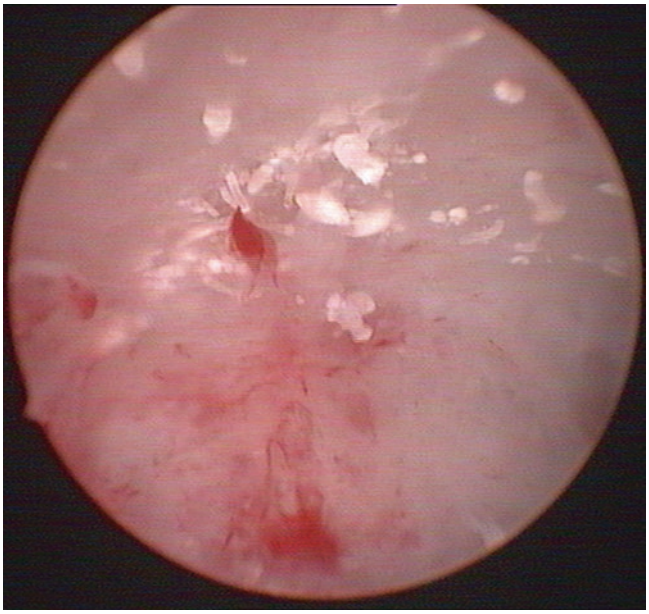

Fig. 11.20 Multiple tubercular deposits on the anterior wall

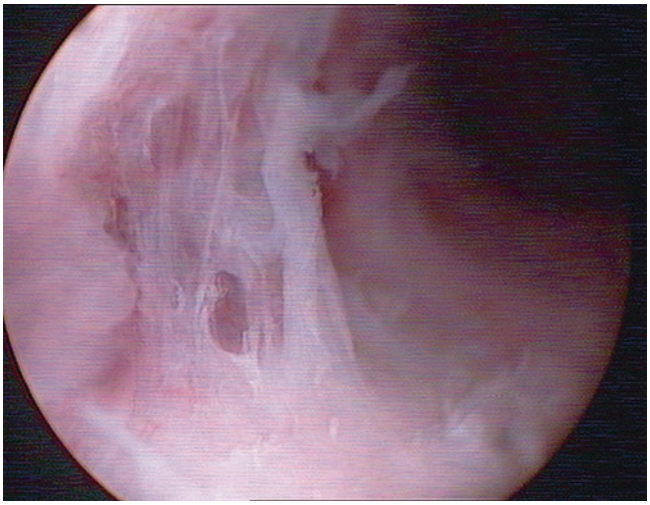

Fig. 11.21 Adehsions endocervical canal

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TBC and Hysteroscopy

12

Sushma Deshmukh

12.1 Introduction

Tuberculosis (TB) has been a major cause of illness and death worldwide for ages and still continues to be so as a major health problem. Genital tuberculosis causes significant pelvic morbidity due to uterine adhesions and infertility in developing countries. Hysteroscopy is a useful modality in diagnosing endometrial TB. It plays an important role in the evaluation of uterine cavity and is of immense help in treating infertility as well as in reproductive failure [1].

Global annual incidence is 8.9 million.

Genital TB is responsible for 5% of all pelvic infections.

Also, there is a potential role of female genital tuberculosis in infertility. This infection has been implicated in 5–10% of infertility cases. But the range varies from less than 1% in the USA to 10% and may be more than that in developing countries. This is a symptomless disease uncovered during investigations for infertility [2].

Genital organs most frequently affected by tuberculosis in order of frequency are fallopian tubes (95–100%), endometrium (50–60%), ovaries (20–30%), cervix (5–15%), and rarely vulva and vagina (1–2%) [3].

But one of the major problems in diagnosing genital tuberculosis is that the medical fraternity is not enough aware of this entity. Genital tuberculosis is a unique featureless disease which is widely prevalent in developing countries and can cause immense damage before the condition is even suspected.

12.2 Hysteroscopy and TBC

Hysteroscopy is a useful modality in diagnosing endometrial TB. Hysteroscopy, when performed in early follicular phase, may miss the diagnosis due to monthly shedding of the endometrium. Most of the times initial stage goes unnoticed and is unremarkable due to repeated menstruation which minimizes the effect of the disease. Hence the best time for conducting hysteroscopic examination is in premenstrual phase so that any overlying deposits are not missed out.

Hysteroscopy in TBC is very challenging, and one should be careful. Difficulties can be encountered since beginning, i.e., from the entry of hysteroscope through the external orifice till the negotiation through cervical canal and internal os to the uterine cavity.

Many times, entry is easy. With the help of 2.9 mm hysteroscope we can enter through the external orifice with little difficulty.

12.3 Difficulties at External Cervical Orifice

In a previously known patient of stenosis one can use misoprostol 200–400 μg vaginally at bedtime prior to procedure. But in my experience, we can negotiate through the external cervical orifice with the help of 2.9 mm or 1.9 mm hysteroscope and semirigid 5 Fr. scissors and forceps. We can resect the fibrous tissue (Fig. 12.1) or ring and advance further under hysteroscopic guidance.

12.4 Difficulties at Cervical Canal

Mild filmy adhesions can be dissected and cut by blunt adhesiolysis. We can get varied pictures of adhesions. With proper visualization and persistent controlled pressure, we can proceed with distension with the help of scissors and forceps under vision. We can also use bipolar current to dissect tough adhesions. Sometimes we may not get the typical picture of the cervical canal of arbor vitae. We may find blunt cervical canal (Fig. 12.2). Sometimes we notice filmy adhesions with tubercles (Fig. 12.3) or thickened fibrous tissue (Fig. 12.4).

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_12

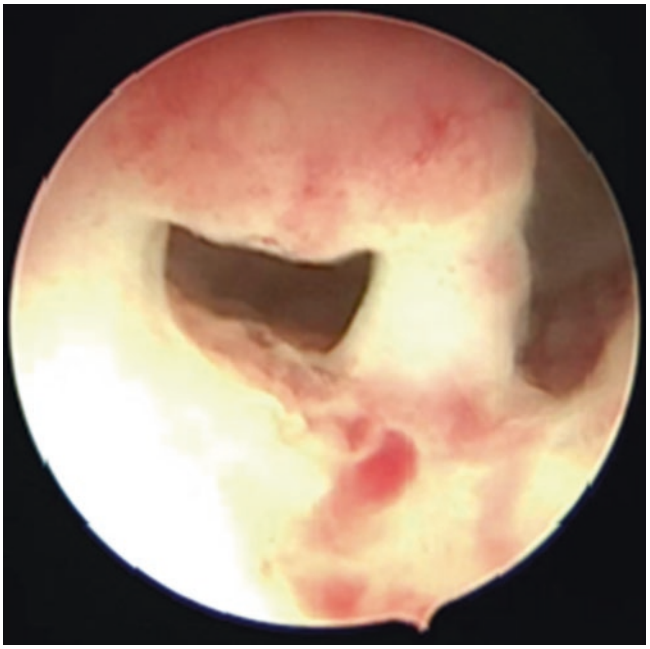

Fig. 12.1 Fibrous band just above the external orifice

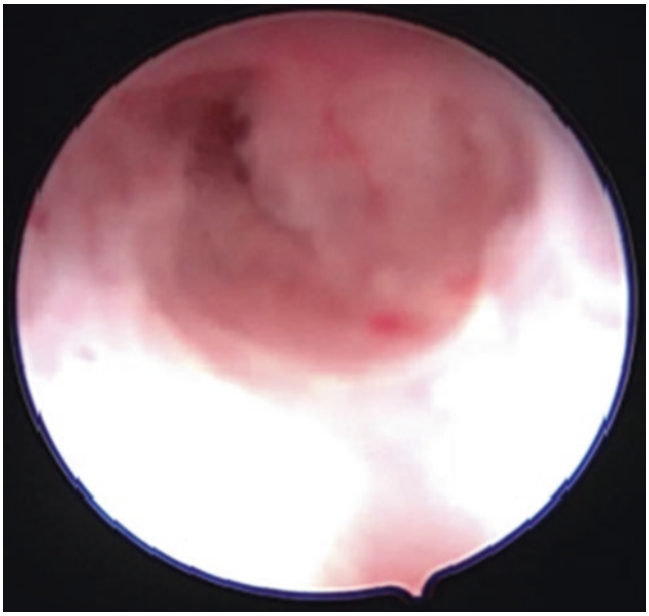

Fig. 12.2 Blunt cervical canal

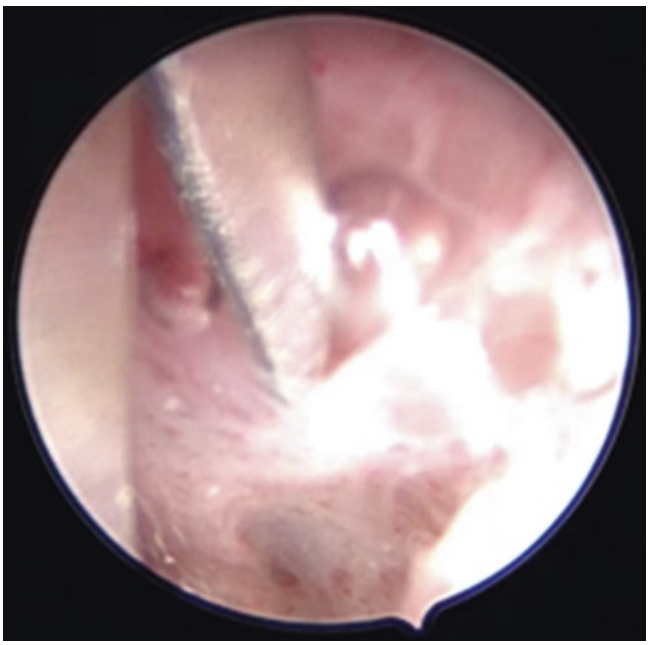

Fig. 12.3 Synechiae and tiny tubercles in cervical canal

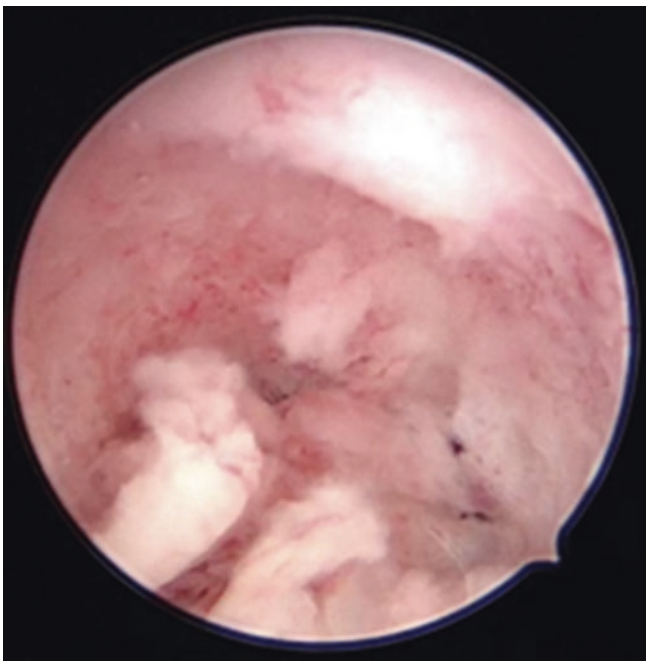

Fig. 12.4 Thickened fibrous tissue in cervical canal and at internal orifice

12.5 Difficulties at Internal Cervical Orifice

The internal orifice has an oval shape with a transverse diameter of 4–5 mm in nulliparous and 7–8 mm in multiparous women. We can negotiate easily with 2.9 mm Bettocchi hysteroscope with anterior–posterior oval diameter. So, we can just rotate the scope and negotiate.

In GTB there can be adhesions (Fig. 12.5) and fibrosis at internal orifice. With the help of hysteroscope we can break and cut the adhesions (Fig. 12.6).

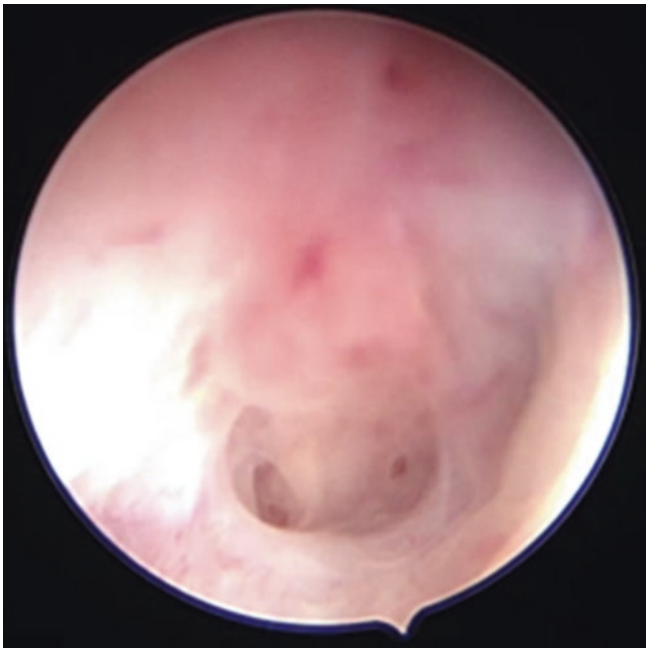

Fig. 12.5 Blunt cervical canal and fibrosis with adhesions at internal orifice

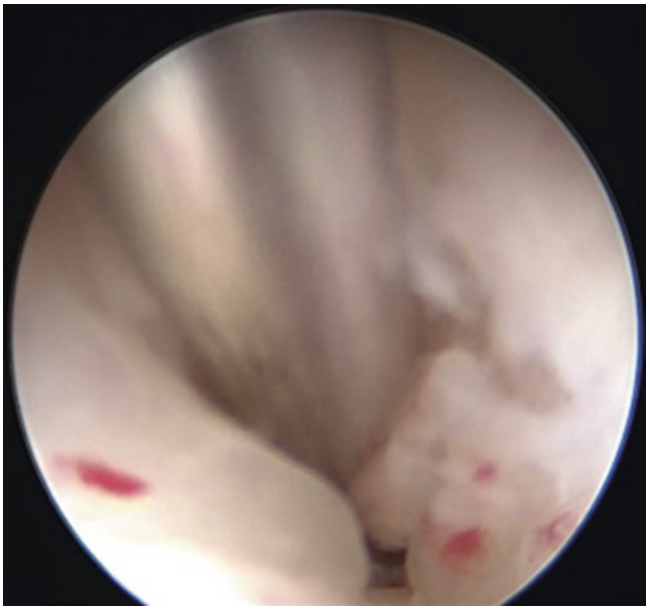

Fig. 12.6 Negotiating through stenosed internal os with forceps

12.6 In the Cavity

In 70% of infertile patients with GTB, cavity is normal with bilateral open ostia and normal-looking endometrium. Classical hysteroscopic finding of endometrial TB is a rough dirty-looking bizarre pale endometrium (Fig. 12.7) with gland openings not seen and with overlying whitish deposits [4].

However, all these signs may not be seen in the same case. Various presentations can be seen. One should be well versed with it.

The findings can be as follows:

- Rough endometrial surface in late proliferative phase.
- The endometrium may be pale looking (Figs. 12.8 and 12.9), thin, or irregular with or without focal areas of hyperemia.
- It may be partially or almost completely covered by multiple irregular whitish deposits.
- Whitish deposits are the most pathognomic of TB; however they may not be always seen.
- These tubercles are often seen on the endometrial surface in the premenstrual phase and are usually located adjacent to the tubal ostia.
- The whitish deposits along with intervening hyperemic endometrium give a geographical map-like appearance (Fig. 12.10).

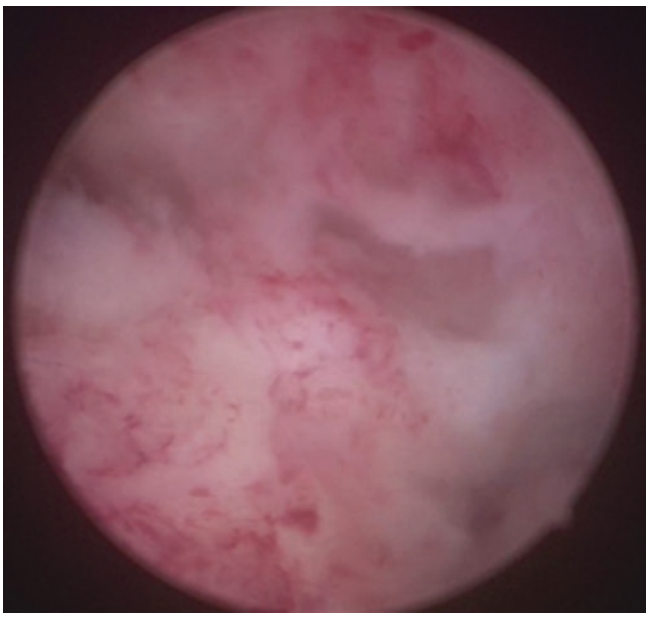

Fig. 12.7 Bizarre dirty endometrium

- Sometimes whitish deposits do not overlie the endometrium; instead they are anchored to filmy adhesions by being impregnated on the same (Fig. 12.11). These filmy adhesions are not shed in menstruation; hence the impregnated deposits are seen even in postmenstrual phase.
- Sometimes tubal ostial fibrosis (Fig. 12.12) and adhesions are seen, so tubal ostia may be blocked or may not be visible on hysteroscopy (Fig. 12.13). We can appreciate intraluminal adhesions in the interstitial part

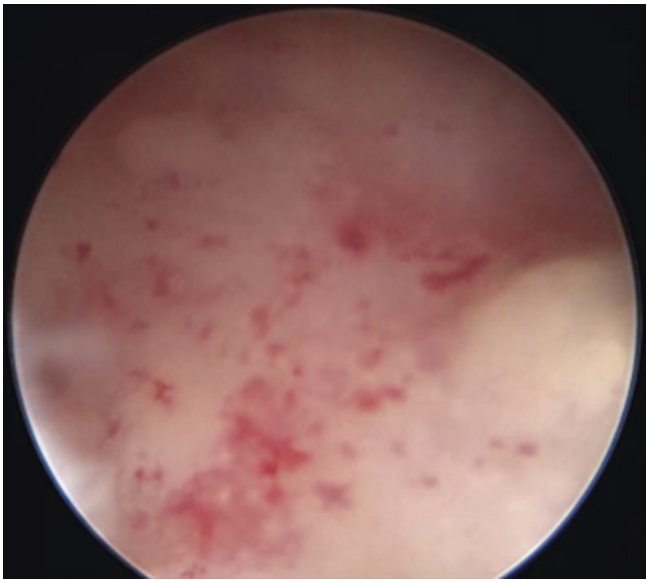

Fig. 12.8 Irregular pale endometrium with hyperemia at places

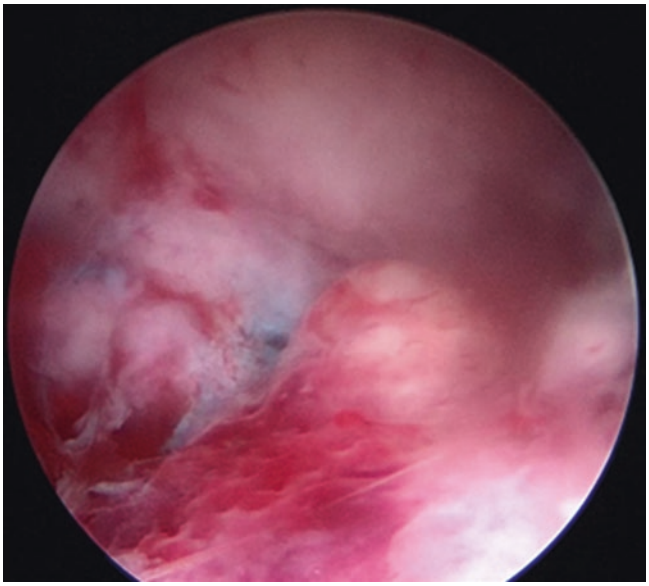

Fig. 12.10 The whitish deposits along with intervening hyperemic endometrium—posterior wall

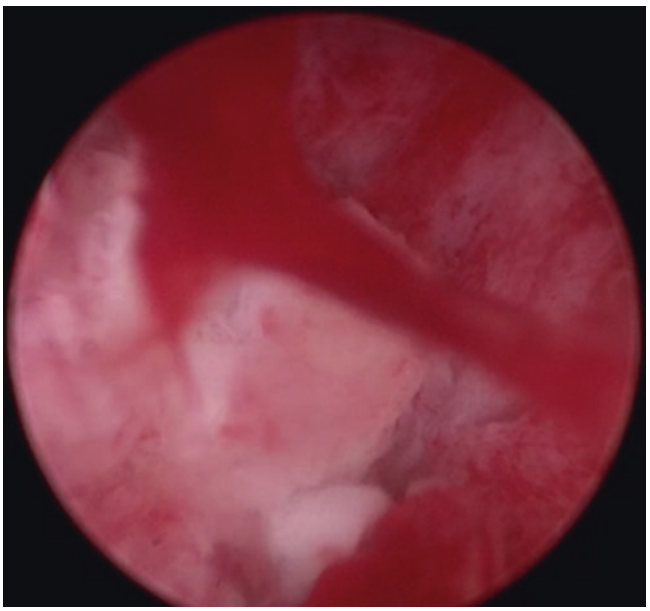

Fig. 12.9 Bizarre pale fluffy endometrium with hyperemia

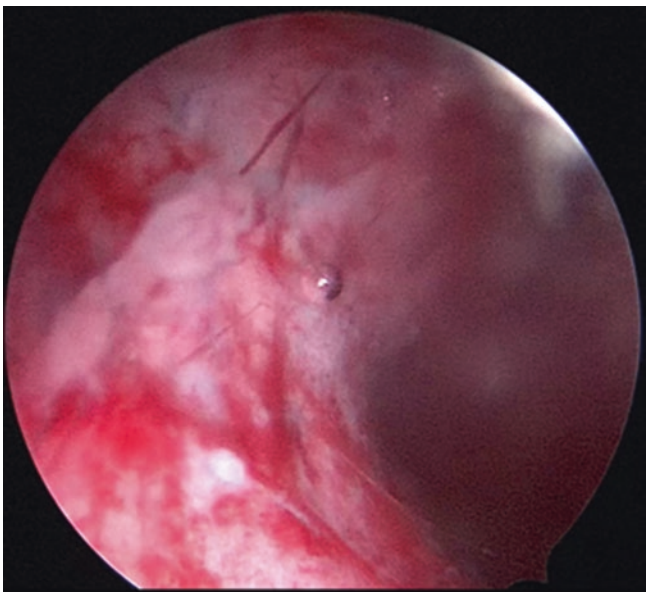

Fig. 12.11 Rough dirty-looking endometrium—flimsy adhesions with tubercle

of the tube by placing the microhysteroscope tip very close to tubal orifice and viewing with a magnification (Fig. 12.14):

- Endocervical scarring is also seen in endometrial TB.
- Granulomas may be present rarely.
- Synechiae when present in the absence of intervention—pale-looking cavity partially or completely obliterated by adhesions of varying degrees.
- Poor distensibility.
- Caseation and ulceration occur in the advanced stage which may lead to adhesion or synechiae formation (Asherman's syndrome).
- The whitish deposits vary in size, have irregular borders, (Fig. 12.15) and peel off easily when touched with hysteroscope. Even in the advanced pelvic tuberculosis caseation fibrosis and calcification are rarely seen in the uterine cavity:
- The cavity may appear small and shrunken (Fig. 12.16).

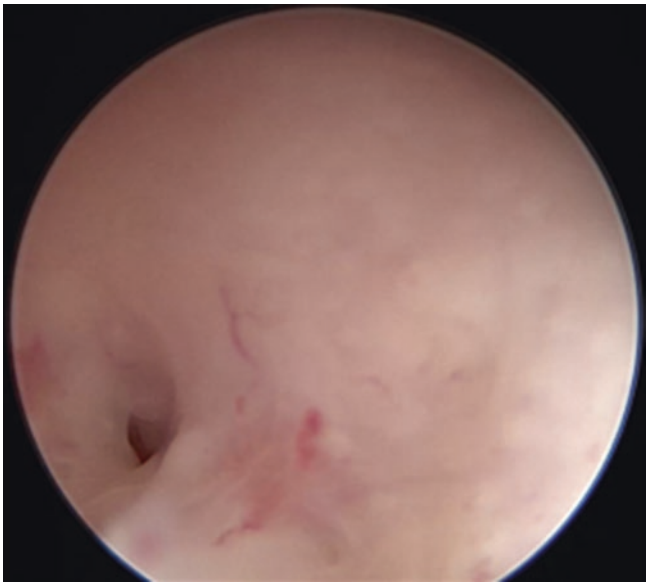

Fig. 12.12 Right ostium adhesions with pale endometrium

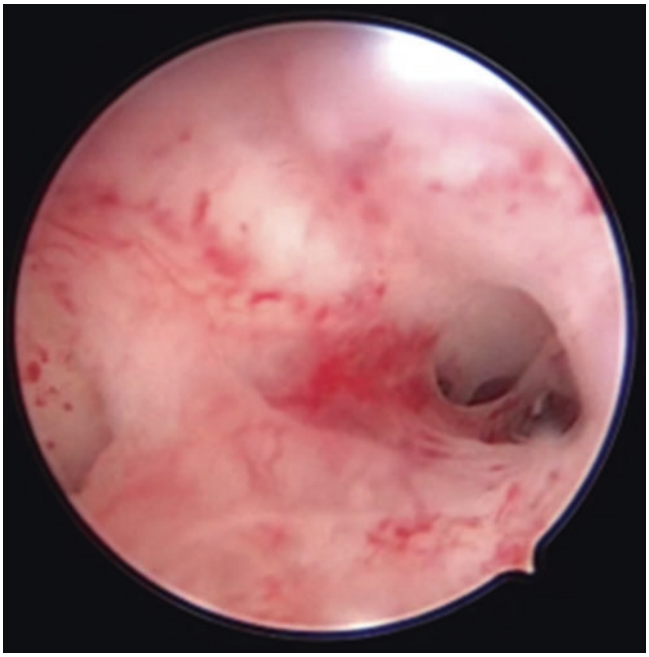

Fig. 12.14 Left ostium covered with flimsy adhesions

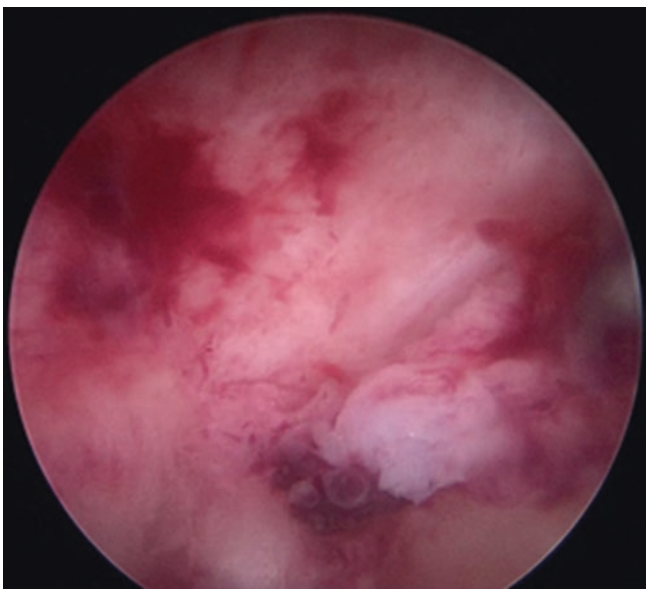

Fig. 12.13 Adhesions over right ostium—at 6 o'clock

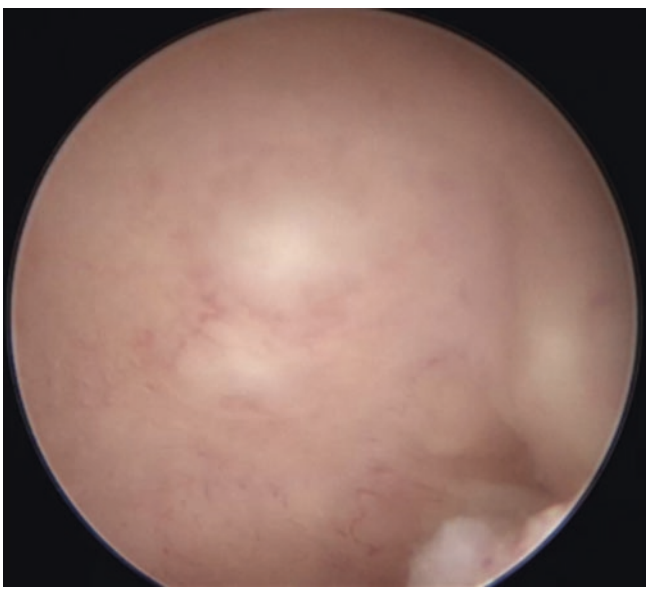

Fig. 12.15 Pale endometrium with tubercles at center

– Very occasionally the cavity is obliterated by extensive fibrosis.
– Starry sky appearance:
  • Sometimes whitish deposits are not seen. But with vital staining with methylene blue (chromopertubation) such deposits are seen. Glistening white, highly reflective deposits against the background of dark blue endometrium are observed. They resemble a "starry sky" appearance. It appears that methylene blue dye is not taken up by the caseous tubercular deposit but is taken up by the surrounding endometrium. The unstained caseous deposit reflects white light (Fig. 12.17) in contrast to the surrounding dark blue endometrium, thereby giving starry sky appearance [5].
  • It is always important to have laparoscopic look in patients with endometrial TB. Most of the time we get various types of presentations depending upon the severity (Figs. 12.18, 12.19, 12.20, and 12.21).

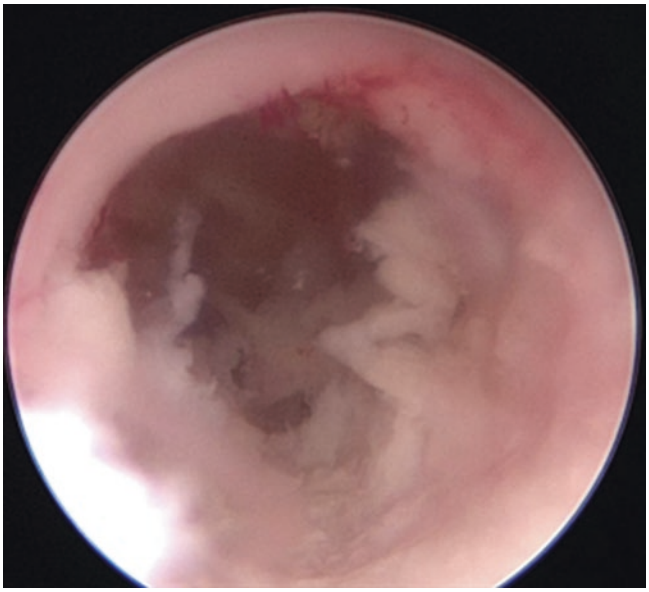

Fig. 12.16 View of uterine cavity from internal orifice—shrunken small cavity

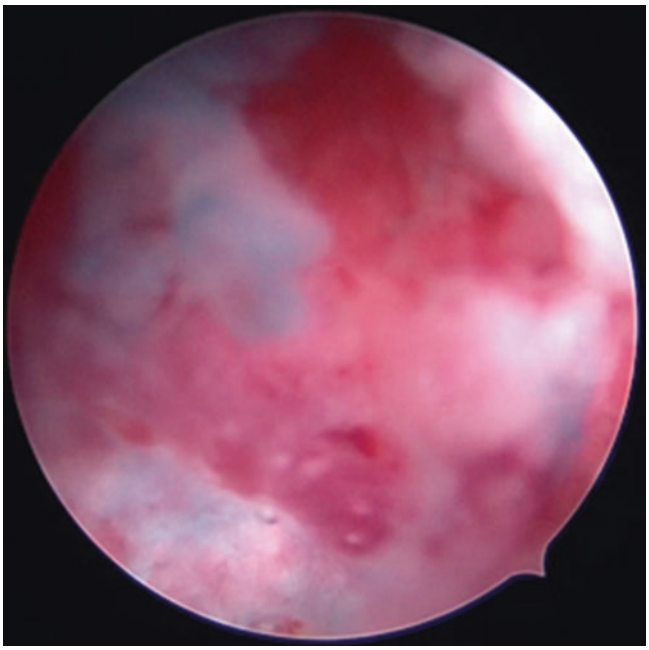

Fig. 12.17 After instillation of methylene blue and white deposits

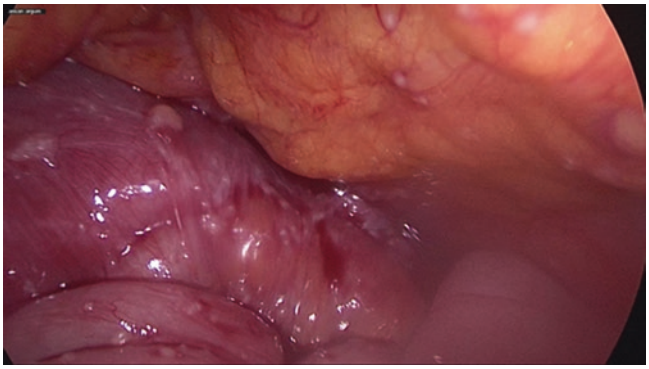

Fig. 12.18 Frozen pelvis—intestines and uterus adherent with tubercles

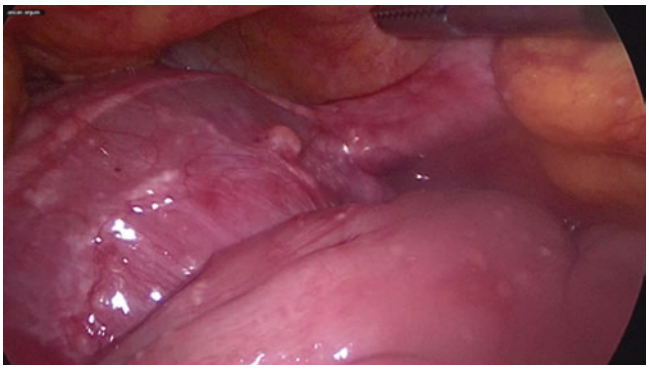

Fig. 12.19 Frozen pelvis—only some part of anterior wall of uterus with right round ligament seen—in the same patient

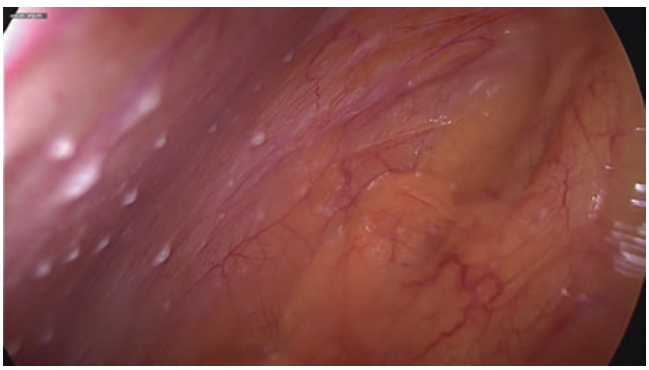

Fig. 12.20 Multiple tubercles on the inner wall of abdomen

12.7 Role of Therapeutic and Second-Look Hysteroscopy

Sometimes patients with genital TB are clinically asymptomatic and while investigating them for their gynecological symptoms they may be incidentally diagnosed as tuberculosis based on hysteroscopic and laparoscopic findings. So, in such patients we can do adhesiolysis (Fig. 12.22). Total corporal synechiae due to tuberculosis carry a very poor prognosis following hysteroscopic synechiolysis [6]. Genital tuberculosis is an important cause of Asherman's syndrome in India [7]. We must be very careful while doing adhesiolysis in such patients as there are chances of perforation and rupture [8].

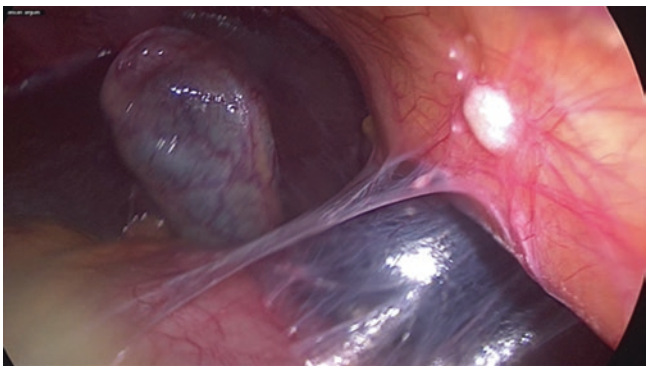

Fig. 12.21 Tubercle with flimsy adhesions near liver

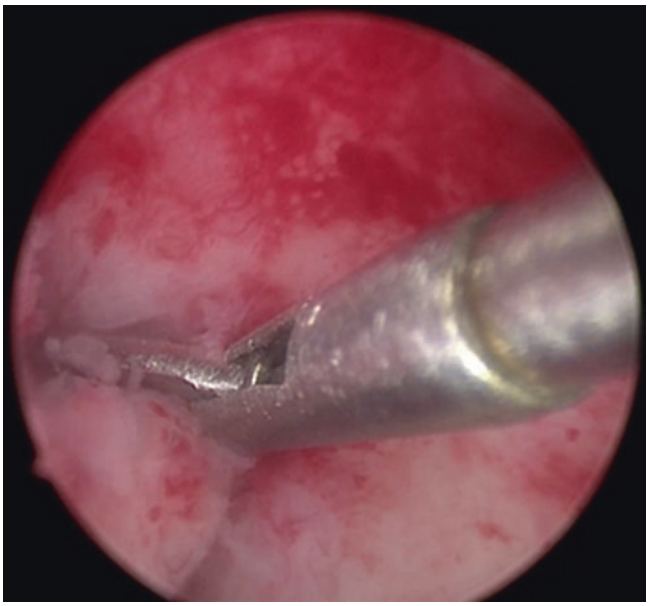

Fig. 12.22 Breaking the synechiae with scissors in endometrial tuberculosis

12.8 Word of Caution

One must be careful while performing hysteroscopy in genital TB as cervix is often constricted and negotiation and dilatation with hysteroscope will be difficult.

There are chances of false passage and perforation.

Many times, hysteroscopy is associated with difficulty and inability to do the procedure due to poor distention of the cavity.

Many studies observed a very high prevalence of Asherman's syndrome in female GTB.

12.9 Advantage of Hysteroscopy

Visual diagnosis: It is always better to have a look over the endometrium as many times there are false-negative histopathological and PCR reports.

We get an opportunity to get the material for histopathological sampling and confirmation of the diagnosis.

In the same sitting we can give diagnostic as well as therapeutic benefit to the patient, e.g., adhesiolysis.

In second-look hysteroscopy we can confirm the benefit of the treatment as well as fertility potential. Genital tuberculosis appears to be an important and common cause of Asherman's syndrome in India, causing oligomenorrhea or amenorrhea with infertility.

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Retained Products of Conception

13

Luis Alonso Pacheco and Laura Nieto Pascual

13.1 Introduction

RPOC is defined as the presence of placental and/or fetal tissue that remains inside the uterus after a spontaneous pregnancy loss (miscarriage), planned pregnancy termination, or preterm/term delivery. The presence of RPOC after a spontaneous pregnancy loss distinguishes an incomplete from a complete abortion (Figs. 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 13.10, 13.11, 13.12, 13.13, 13.14, 13.15, 13.16, and 13.17).

It is estimated that the incidence of RPOC is approximately 0.5% after surgical abortions during the first trimester [1] being more common after medical abortion, increasing its incidence as the gestational age of the termination of pregnancy advances [2].

The symptoms can vary between patients related to the amount of tissue retained, the vascularization of the products, and the length of time that has been retained. The main symptom is vaginal bleeding that can range from spotting to heavy vaginal bleeding that can result in acute anemia. Other frequent symptoms are uterine tenderness, pelvic pain, and, in cases of infection, fever. Significant uterine tenderness, heavy vaginal bleeding, cervical dilation, uterine enlargement, cervical motion tenderness, or signs of systemic infection should prompt further evaluation for RPOC.

As a general rule, the presence of RPOC should be suspected in any case presenting with excessive bleeding that occurs after an abortion, miscarriage, or delivery (both vaginal and cesarean section).

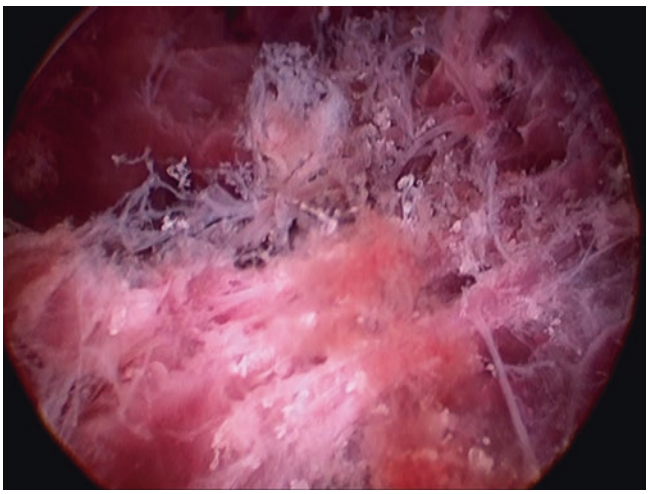

Fig. 13.1 Detailed view of "red" chorionic villi

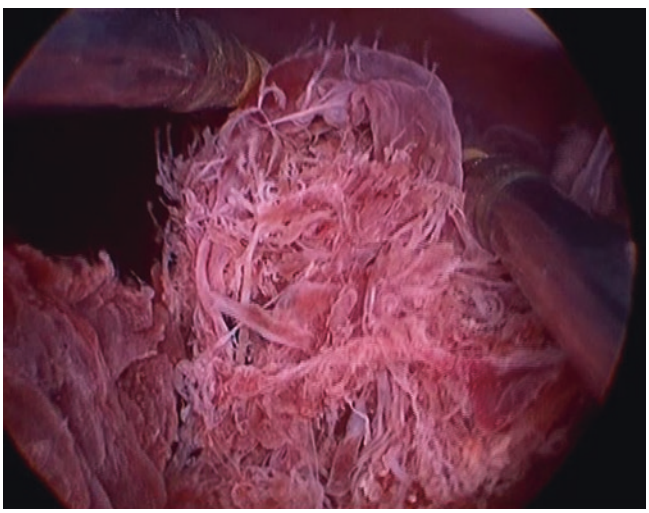

Fig. 13.2 Removing retained products of conception using a loop

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_13

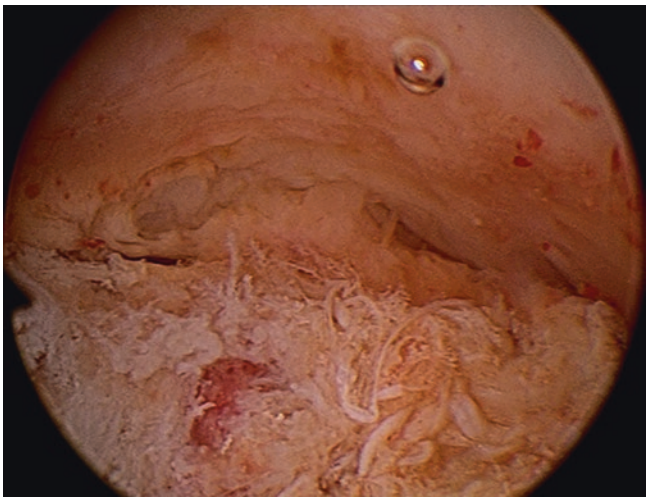

Fig. 13.3 Type I RPOC (pale color)

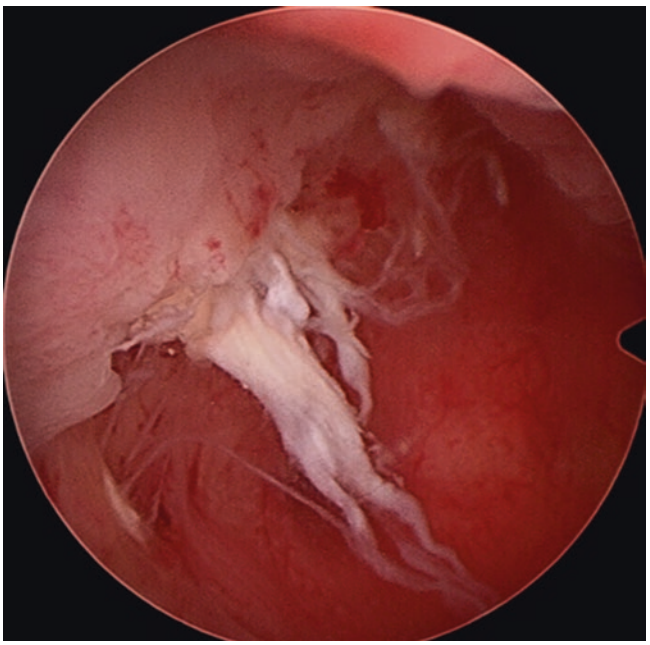

Fig. 13.4 RPOC in which no structure is defined

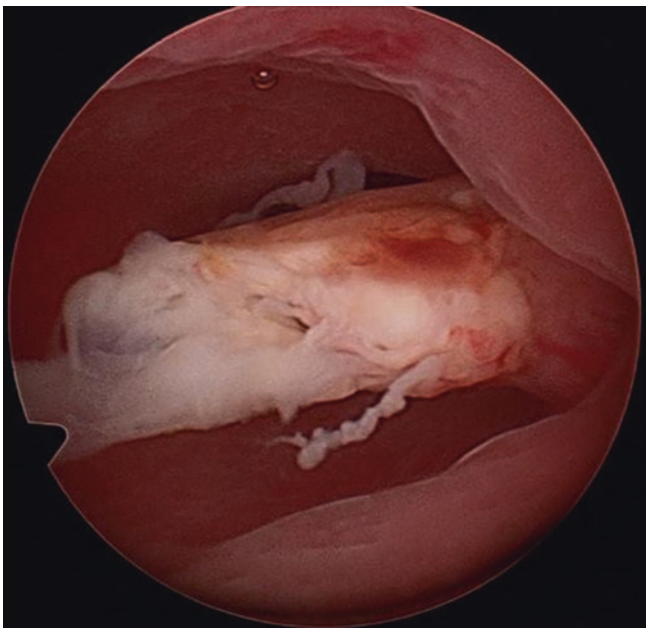

Fig. 13.5 RPOC has a focal implantation

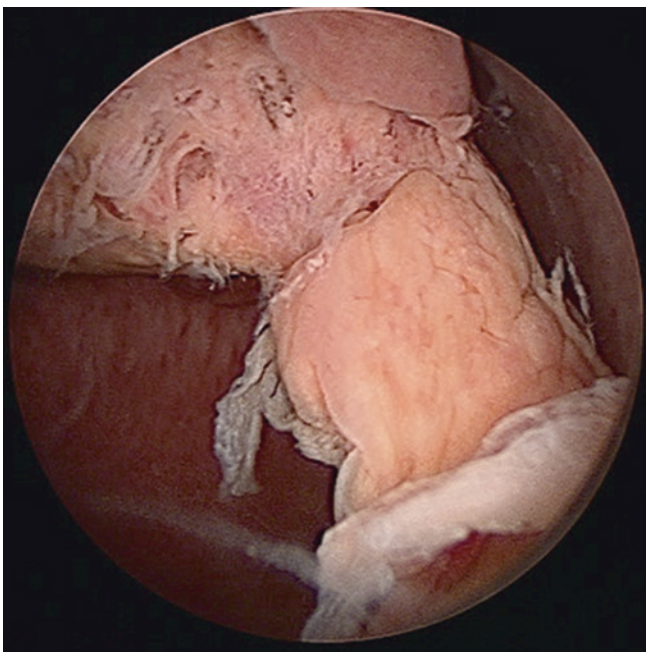

Fig. 13.6 White mass with no identifiable structures

13.2 Diagnosis

The accurate diagnosis of RPOC represents a challenge since it is considered normal to have some bleeding and discomfort or pain after the termination of a pregnancy, regardless of the week of gestation at which the termination occurs.

The gynecological exam reveals vaginal bleeding coming from the uterine cavity that, as we have mentioned previously, can vary in quantity from mild to massive bleeding. Occasionally, blood clots or debris can be seen protruding through a dilated external cervical os [3]. The bimanual examination helps us to determine the uterine size that is frequently large.

The determination of serologic levels of b-hCG usually has a limited value since it is usually maintained >5 IU for a few days after the end of pregnancy. It can persist elevated depending on the hormonal activity of the retained products that occasionally do not have hormonal activity.

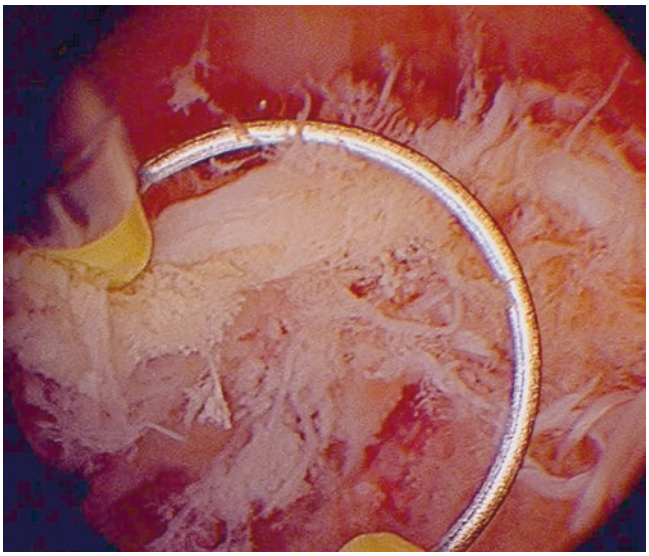

Fig. 13.7 Type I RPOC

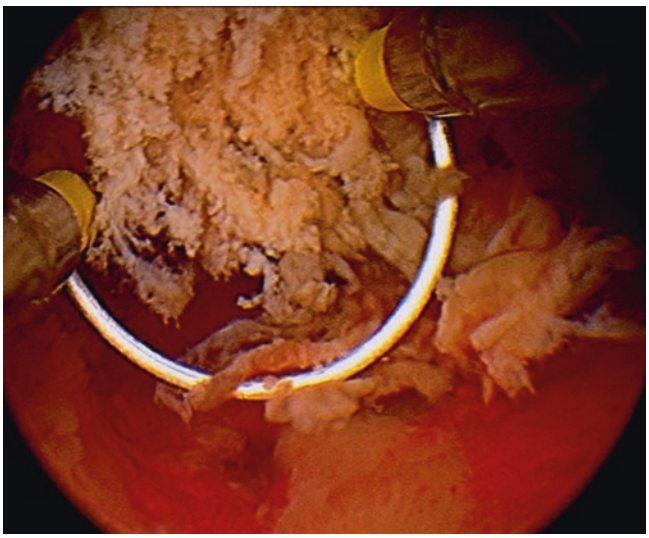

Fig. 13.8 Detailed view of white chorionic villi

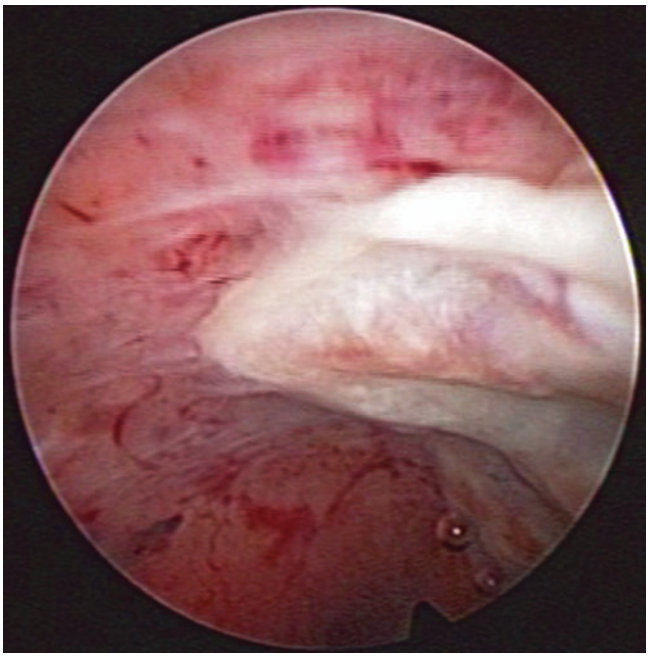

Fig. 13.9 Focal implantation of type 0 RPOC

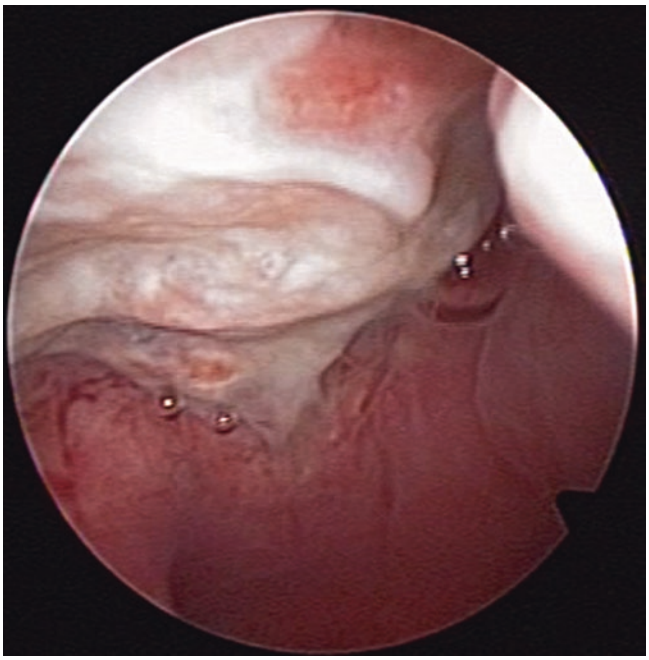

Fig. 13.10 Type 0 is seen as a white mass

Without a doubt, ultrasound is the main imaging modality for the diagnosis of RPOC. The visualization of a mass inside the endometrial cavity is the most important finding in the ultrasonographic diagnosis of RPOC and the absence of debris inside the uterine cavity with the visualization of a thin endometrial stripe excludes this pathology with a predictive value of 100% [4].

After the delivery of a viable fetus or an abortion, the endometrium undergoes a series of changes that are part of the mechanism of evacuation of the uterus; after this initial period of bleeding, the absence of an intracavitary mass 8 weeks postpartum or 2 weeks postabortion rules out the presence of RPOC [5] while an endometrial thickness greater than 13 mm is considered as a pathognomonic diagnostic criterion for the echographic diagnosis of this entity [6].

Occasionally, the retained products have high vascularization; with the use of Doppler technology this vascularization can be appreciated not only in the retained products of conception but also affecting the underlying myometrium in

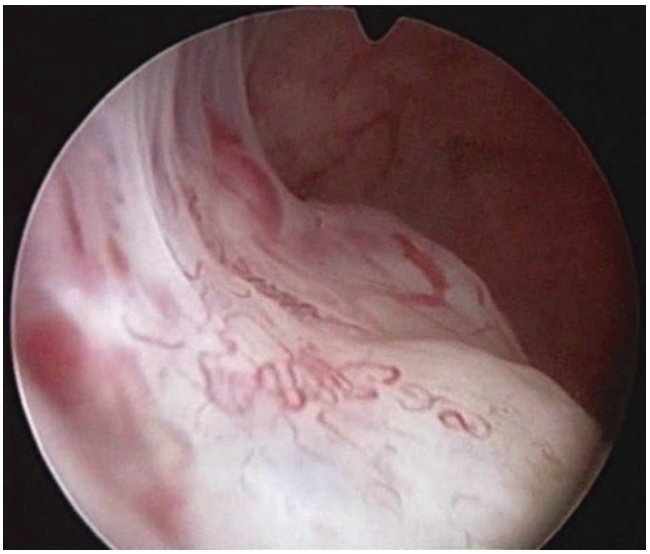

Fig. 13.11 Old RPOC (3 years)

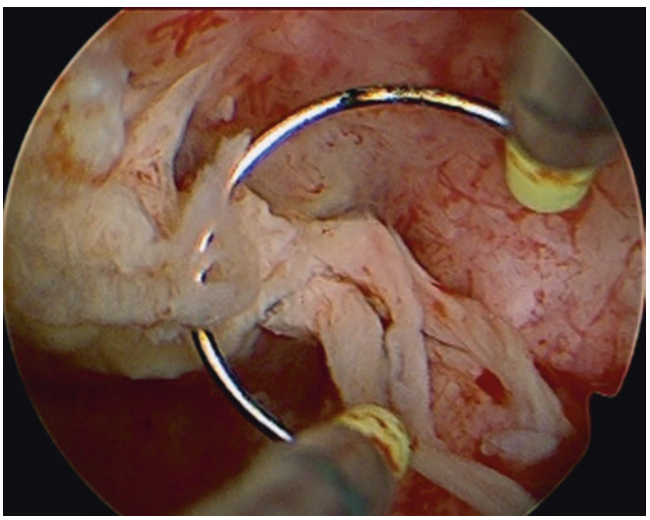

Fig. 13.12 White intrauterine structure

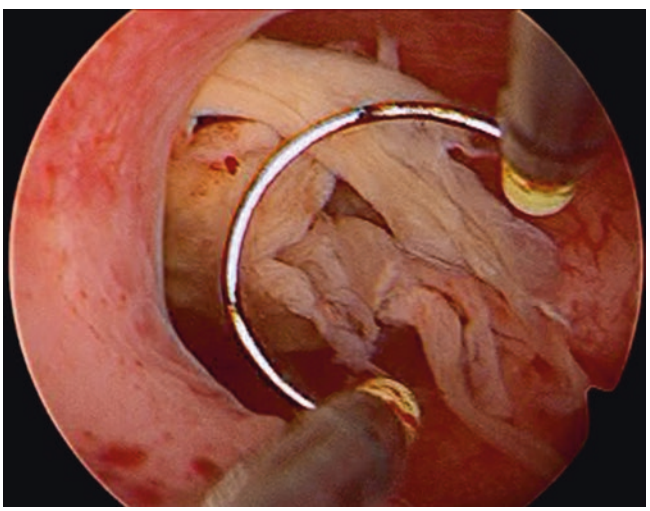

Fig. 13.13 White material corresponding to type 0 RPOC

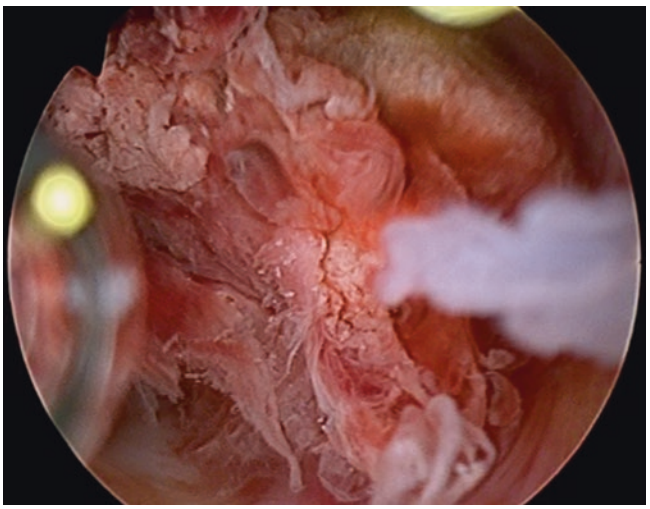

Fig. 13.14 RPOC filling the whole uterine cavity

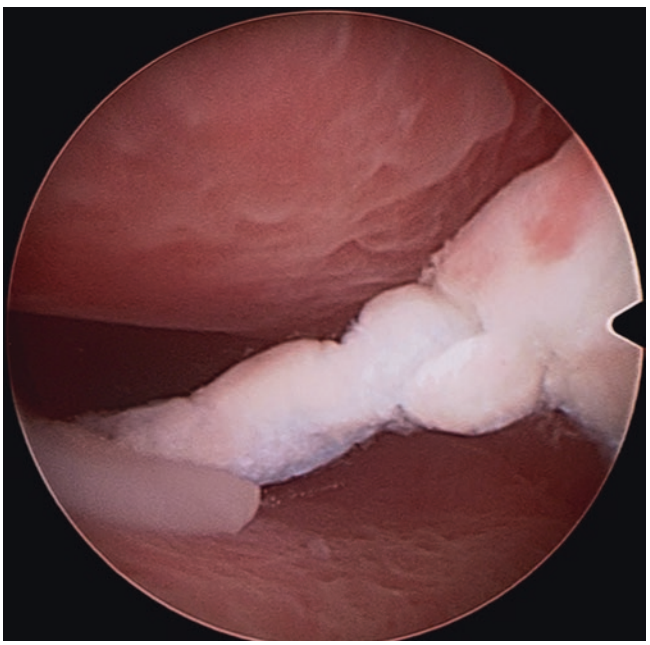

Fig. 13.15 Type 0 RPOC

the implantation area. Some authors argue that the implantation area remains highly vascularized during the postpartum and postabortion period of uterine involution [4].

Hysteroscopy is considered the gold standard for the diagnosis of intrauterine pathology including gestational retained products. The hysteroscopic appearance of this pathology varies depending on the involution, vascularization, and degree of necrosis of the trophoblastic retained tissue, which results in no single hysteroscopic pattern. This is because the retained tissue undergoes a process of involution over time that makes changes in their macroscopic appearance, so it is important to know the different macroscopic aspects that this pathology presents.

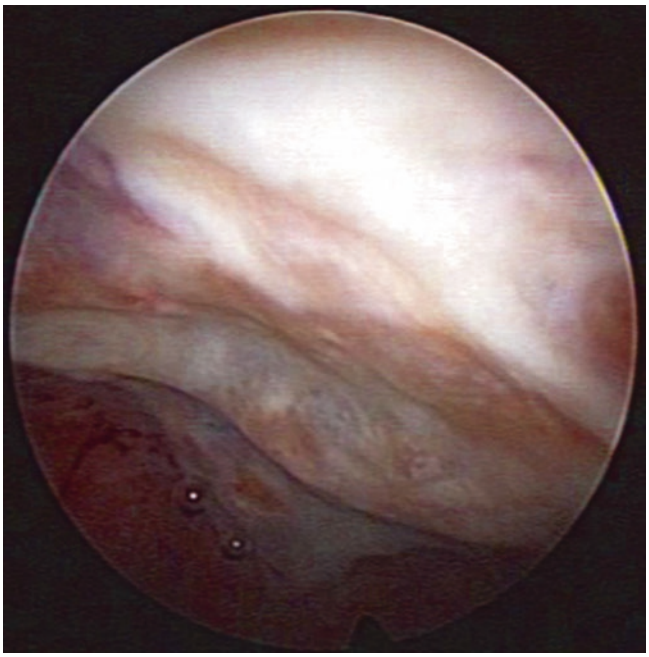

Fig. 13.16 White intrauterine mass

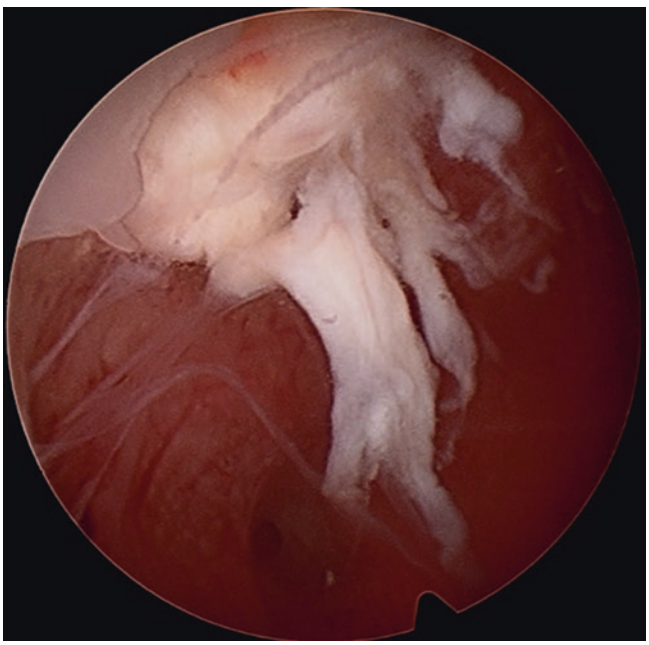

Fig. 13.17 No structures are defined

The Gutenberg classification correlates the different ultrasound patterns with the hysteroscopic appearance of RPOC, which allows to anticipate the complexity and degree of difficulty that may be encountered at the time of uterine evacuation [7].

This classification distinguishes four different patterns of ultrasound characteristics, based on the sonographic appearance of the intracavitary retained products, and the intracavitary and myometrial vascularity of the implantation zone. The ultrasound classification distinguishes (Table 13.1):

Table 13.1 Gutenberg classification of *ultrasonographic* patterns of retained products of conception

Type	Intrauterine echogenic mass	Intracavitary vascularization	Myometrial vascularization
Type 0	Homogeneous	No	No
Type I	Heterogeneous	Minimal	No
Type II	Heterogeneous	Highly	No
Type III	Heterogeneous	Highly	Present

Table 13.2 Gutenberg classification of *hysteroscopic* patterns of retained products of conception

Type	Chorionic villi structure	Vascularity	Attachment
Type 0	Not defined	Normal	Loose
Type I	Well defined avascular (white)	Normal	Focally
Type II	Well defined vascular (red)	Mild vascular dilatation	Focally some loose and dense attachment
Type III	Well defined vascular (red)	Severe vascular dilatation, aneurysms, and AV shunt	Densely attached

- *Type 0:* The presence of a bright echogenic intrauterine mass (white), homogeneous and completely avascular.
- *Type I:* Heterogeneous echographic pattern with different echoes and minimal vascularization at intracavitary level
- *Type II:* Heterogeneous echographic pattern with different echoes and highly vascularized at intracavitary level
- *Type III:* Heterogeneous echographic pattern with different echoes and highly vascularized areas at both intracavitary and myometrial levels of the implantation zone

The Gutenberg classification differentiates four ultrasound patterns that are based on retained tissue echogenicity as well as vascularization at both the intracavitary and the myometrial levels. The tissue sonographic appearance can undergo variations over time due to degenerative tissue modifications.

The echographic patterns referred above have a direct correlation with the hysteroscopic patterns observed in these patients. Thus, the Gutenberg classification also distinguishes four hysteroscopic patterns (Table 13.2):

– Type 0: An intracavitary whitish mass is observed in which virtually no structure is defined.
– Type I: Chorionic villi are appreciated, well defined but whitish due to the scarce vascularization of this tissue.
– Type II: Vascularized chorionic villi are observed, modifying the color making them reddish.

– Type III: The aspect of the chorionic villi is similar to the hysteroscopic pattern of type II; the difference is in the area of implantation of the tissue that presents vascular dilatations, aneurysms, and AV shunts.

The hysteroscopic patterns are very diverse and have been classified in four types that vary according to the process of involution experienced by the retained products. Except in type 0, in which no known structures are identified, the rest of the types show the presence of identified chorionic villi with different degrees of vascularization.

The definitive diagnosis is established by the identification of chorionic villi in the pathology study of the retained tissue material. These chorionic villi can have a normal structure or present hyaline or necrotic degeneration giving place to the so-called ghost villi.

13.3 Treatment

The treatment is generally dictated by the patient's hemodynamic condition, the gestational age that resulted in RPOC, the amount of product retained, and the experience of the physician dealing with the condition.

Expectant management could be considered in women with RPOC clinically stable with no evidence of infection. The reported success rates range from 50% to 85% at 1–2 weeks of follow-up, and up to 90% when subjects are followed for 6 weeks.

Different medical treatments have been described to facilitate the evacuation of RPOC. Misoprostol is one of the most widely used medications and has been shown to be effective in more than 90% of incomplete first-trimester abortions. It is reasonable to consider medical management in any stable patient with RPOC.

The physical evacuation of RPOC through the technique of dilatation of the cervical canal and uterine curettage, either with fenestrated sharp curette or by suction with aspiration cannula, continues to be the most widely used evacuation method in clinical practice. Due to the focal nature of the pathology and the fact that uterine curettage is a blind technique, there is risk of incomplete uterine evacuation, which has been reported to be as high as 20.8% after performing conventional curettage [8]. Moreover, this technique, when performed blindly, not only can produce an incomplete evacuation but also increases the possibility of injury to surrounding healthy endometrial tissue; performing a uterine curettage can damage the basal layer of the endometrium favoring the development of intrauterine adhesions or even Asherman's syndrome. The incidence of uterine adhesions in women who undergo repeated curettage for the evacuation of RPOC is reported at 40%.

Hysteroscopic evacuation of RPOC is a feasible, safe, and effective technique that prevents injury to surrounding healthy endometrium, which clearly reduces the possibility of complications such as intrauterine adhesion formation or incomplete evacuation of products of conception. There are different tools and techniques for removal of RPOC; their use depends on the availability and physician's experience. Any hysteroscopic technique is useful for the extraction of intrauterine retained products of conception, although in cases where there is high vascularization we recommend the use of the resectoscope provided with energy that allows to selectively cauterize the blood vessels when needed. Special care should be taken with type III RPOC cases, since bleeding can be profuse, increasing the chance of severe complications.

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Endometrial Hyperplasia

14

Jorge Enrique Dotto and Miguel A. Bigozzi

14.1 Definition and Epidemiology

Endometrial hyperplasia (EH) represents a spectrum of irregular morphological alterations, whereby abnormal proliferation of the endometrial gland results in increased thickness of endometrial tissue with alterations of glandular architecture (shape and size) and in an increase in gland-to-stroma ratio when compared to endometrium from the proliferative phase of the cycle [1, 2]. Most EHs develop in a background of chronic stimulation of the endometrium by estrogens unopposed by a progestin, occurring secondary to a number of possible conditions.

Endometrial hyperplasia is considered as a precursor to type 1 endometrial carcinoma(estrogen dependent) of which the endometrioid histological subtype accounts for 75%, and typically represents low-grade tumors which are often amenable to surgical treatment [3, 4].

Type 2 endometrial cancer tends to be estrogen independent and includes the clinically aggressive serous and clear cell histological subtypes, more often associated with endometrial atrophy [5–7].

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EH has a prevalence of 1.3% in women of fertile age, and 15% in those of postmenopausal age, with a peak incidence from 50 to 60 years of age.

14.2 Classification

There are two different systems to classify endometrial hyperplasia, the World Health Organization (WHO) schema [8] and the endometrial intraepithelial neoplasia (EIN) [9]. The WHO classification system, which is the most commonly recognized system, uses cellular complexity, crowding of the endometrial gland, and presence of cytological atypia to categorize pathologies as simple or complex hyperplasia, with or without atypia [10–12]. The complexity of the WHO classification system has prompted improvement of an alternative system, the *endometrial intraepithelial neoplasia* (EIN). The EIN simplified the histological classification into two groups: a combined category for *simple hyperplasia and complex hyperplasia,* referred to as "hyperplasia," and a combined category for *atypical hyperplasia* and *well-differentiated adenocarcinoma*, called "endometrial intraepithelial neoplasia" [9]. EIN includes architectural gland crowding, cytological atypia, and maximum linear dimension of the lesion exceeding 1 mm while excluding cancer and mimics. EIN classification system is easy and more reproducible, helping clinicians to select treatment options.

The risk of developing endometrial cancer is highest in atypical hyperplasia.

14.3 Risk Factors

Endometrial hyperplasia's risk factors are the same as those of endometrial cancer type1. Several conditions associated with steroid hormone disbalances, as chronic anovulation (PCO syndrome), early menarche, late onset of menopause, nulliparity, and prolonged exogenous estrogen exposure

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_14

without concomitant progestin balance, cause increased risk of endometrial hyperplasia.

Tamoxifen treatment may result in endometrial thickness and polyps, leading to irregular endometrial linings that are associated with endometrial hyperplasia and endometrial cancer [10].

Women with hereditary non-polypoid colorectal cancer (Lynch syndrome) may have complex atypical endometrial hyperplasia at an earlier age and altered estrogen levels which affects expression of DNA repair genes [11–13].

Diabetes, hypertension, and obesity are also associated with increased endometrial hyperplasia risk. Obesity in fact causes elevated estrogen levels and chronic inflammation that can promote hyperplasia and cancer.

14.4 Diagnosis

Endometrial hyperplasia is often suspected in women with abnormal uterine bleeding. More than 90% of patients with endometrial hyperplasia have AUB. However, confirmation of diagnosis requires histological analysis of endometrial tissue.

14.5 Hysteroscopy

Microhysteroscopy is a safe and nontraumatic technique that provides a satisfactory assessment of the uterine cavity, and it is an effective tool for the detection of premalignant lesions and early stages of endometrial cancer. The current state of development of the microhysteroscope provides a high-quality image of the endometrium [1–5] that allows an approximation to the histological diagnosis of these lesions. In every case, the final diagnosis is histological; however, we consider that our classification of microhysteroscopic images according to the degree of suspicion is both a useful resource for effective communication among the attending gynecologist, the hysteroscopist, and the pathologist and a useful guide for selecting the cases and sites for endometrial biopsies [2, 9].

There are morphological criteria to be used as hysteroscopic predictors of endometrial hyperplasia. These criteria have not been defined based on scientific evidence resulting from controlled randomized clinical trials (RCTs). The morphological criteria derived on hysteroscopic inspection are subjective, operator related, and poorly reproducible. In the diagnosis of endometrial hyperplasia hysteroscopy sensitivity is no more than 78% [14].

Hysteroscopy is the technique that includes patients with AUB that needs biopsy and helps to direct under visual central biopsy compliance and reliability changes completely.

Endometrial hyperplasia and cancer are affecting a monolayer epithelium (endometrium). Abnormalities and morphological alterations related to endometrial hyperplasia and cancer are visible in all cases. Hysteroscopy is often not able to make differential diagnosis but is able in 100% of patients to suspect an "atypical area" to be biopsied [15].

Based on our experience and the nomenclature used by Italian authors [13, 14], we developed the following *classification of hysteroscopic images*:

1. Normal hysteroscopy
   (a) Reproductive-aged women
      - Proliferative phase
      - Luteal phase
   (b) Postmenopausal women: atrophic endometrium
2. Benign lesions
   (a) Endometrial changes due to hormone therapy
   (b) Myomas (submucous and intramural)
   (c) Adenomas endometrial polyps
   (d) Endometritis
   (e) Synechiae
   (f) Foreign bodies
   (g) Uterine malformations
   (h) Placental remnants; placental polyps
3. Low-risk hyperplasia
4. High-risk hyperplasia
5. Carcinoma and other malignant tumors

The endometrial mucosa is heterogeneous in appearance with projections and marked vascularization. The current histological classification groups hyperplasias as simple, including simple hyperplasia and glandular cystic hyperplasia of the old classification system; complex hyperplasia, previously called adenomatous hyperplasia; and atypical hyperplasia [3–8].

This classification is concomitant with a range of microhysteroscopic aspects. Endometrial hyperplasia is defined as an exuberant irregular development of endometrial mucosa, which can be either focal or generalized.

14.5.1 Low-Risk Hyperplasia

The appearance of simple hyperplasia is similar to that of a normal endometrium, with normal glandular distribution, but thicker. This can be measured through the depression (>7 mm) produced by the distal tip of the endoscope (Fig. 14.1).

In classic glandular cystic hyperplasia (GCH) the opening of the glands forms a relief including small cysts. This relief is sometimes related to cystic atrophy (apparently due to involution or regression of some CGH features) (Fig. 14.2).

This type of hyperplasia produces several different images.

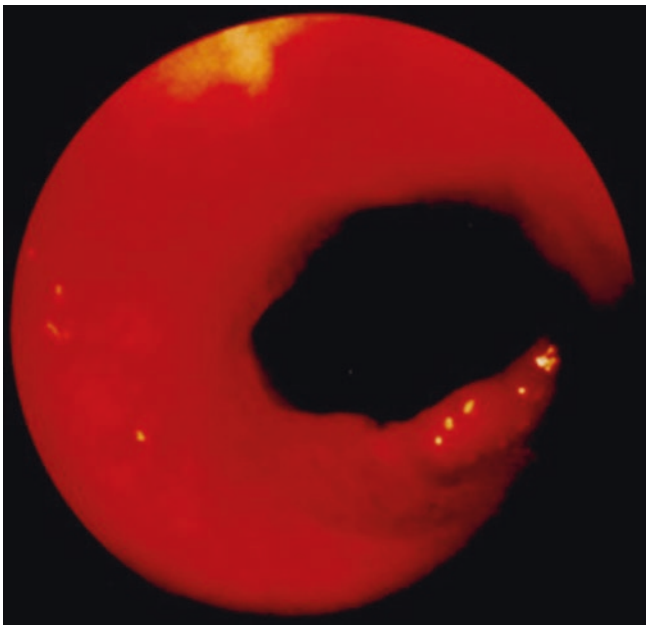

Fig. 14.1 Low-risk hyperplasia. Small, whitish, protruding, well-defined area in right horn ostium. Microhysteroscopic diagnosis: low-risk hyperplasia. Histopathologic diagnosis: simple hyperplasia

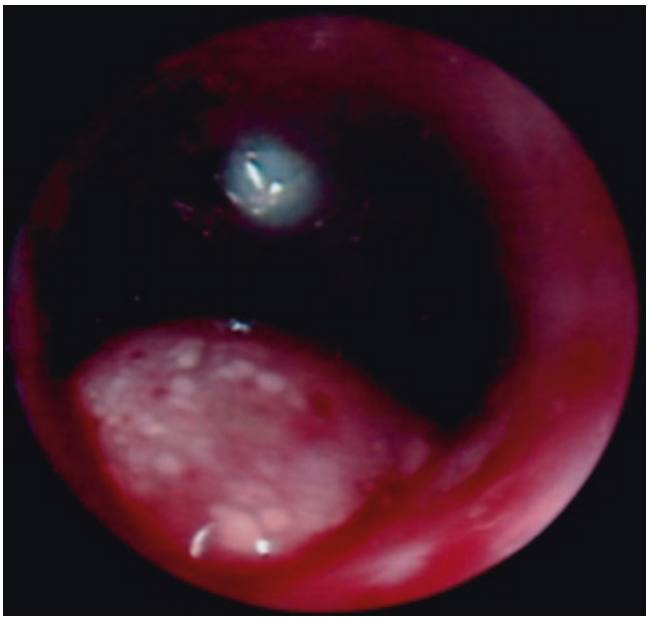

Fig. 14.3 LRHY. High-risk hyperplasia. Extension towards the endocervical duct can be observed. HP: Complex hyperplasia

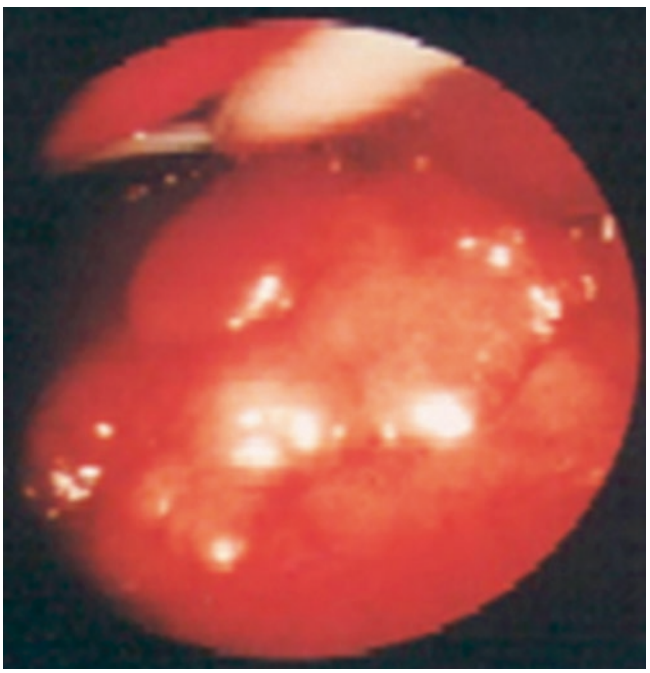

Fig. 14.2 Low-risk HY. Patient with an IUD with exuberant endometrial proliferation and small cyst formation. Microhysteroscopic diagnosis: IUD + low-risk hyperplasia. Histopathologic diagnosis: IUD + simple hyperplasia

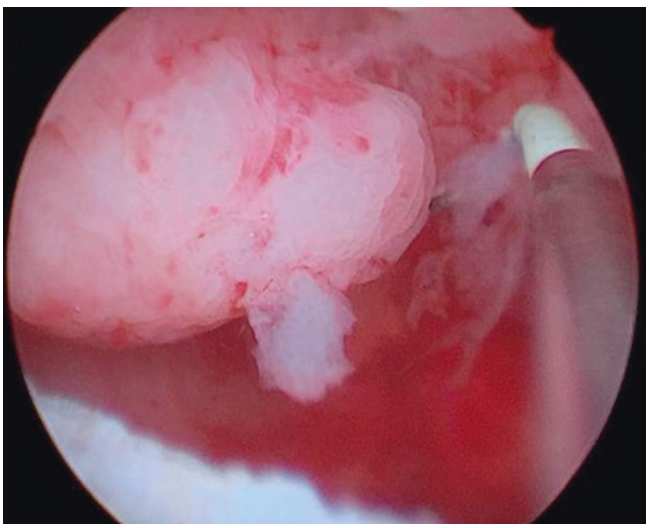

Fig. 14.4 Image: low-risk endometrial hyperplasia. Pathology: simple hyperplasia

In polypoid hyperplasia, several polyps of different sizes can be observed. They present marked vascularization and interpapillary bridges [16–18] (Figs. 14.3, 14.4, 14.5, 14.6, and 14.7).

14.5.2 High-Risk Hyperplasia

The endometrial surface shows polypoid proliferation as well as interpapillary bridges that can be evident on a hemorrhagic background. Only through histology can this condition be appreciated. Adenomatous hyperplasia has an irregular mammillated surface, and an imprint is left by the hysteroscope on the surface [19–21] (Figs. 14.8, 14.9, 14.10, 14.11, 14.12, 14.13, 14.14, 14.15, 14.16, 14.17, 14.18).

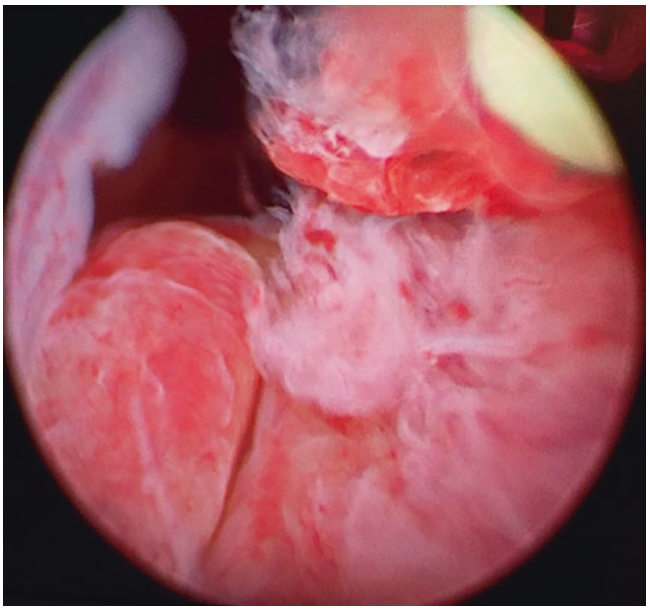

Fig. 14.5 Image: LRH. Pathology: simple hyperplasia

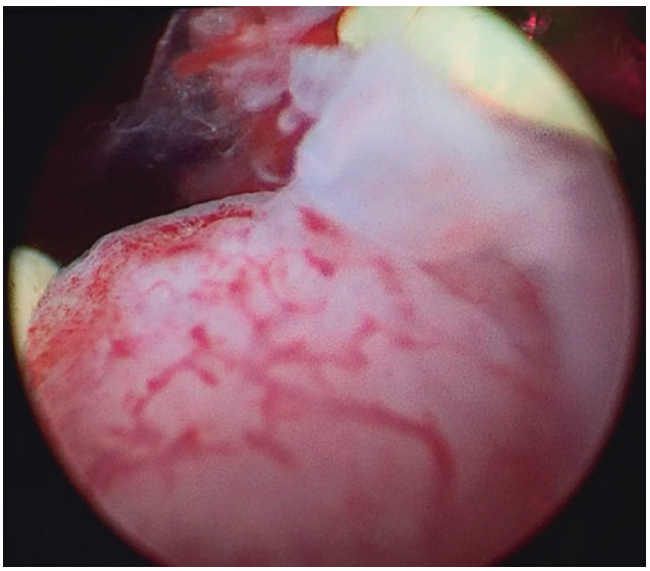

Fig. 14.6 LR polypoid hyperplasia. Pathology: simple polypoid hyperplasia

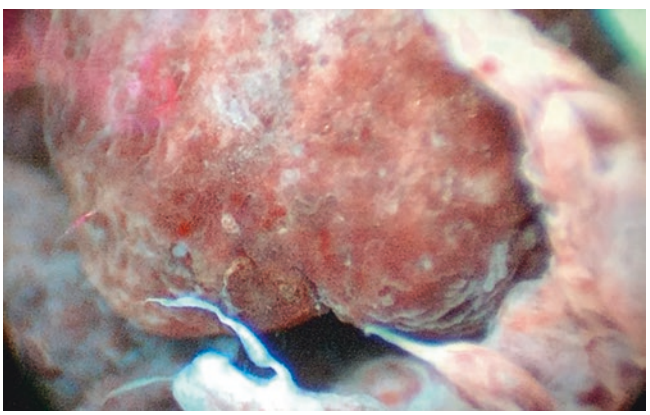

Fig. 14.7 Image: LRH. Pathology: polypoid hyperplasia

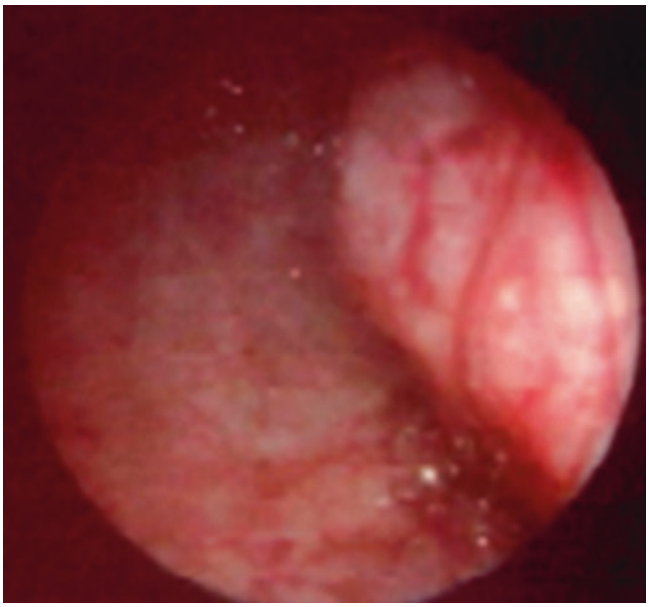

Fig. 14.8 High-risk hyperplasia. Polypoid structure. Background with irregular mammillated surface. Microhysteroscopic diagnosis: High-risk polypoid hyperplasia. HP: complex hyperplasia (adenomatous)

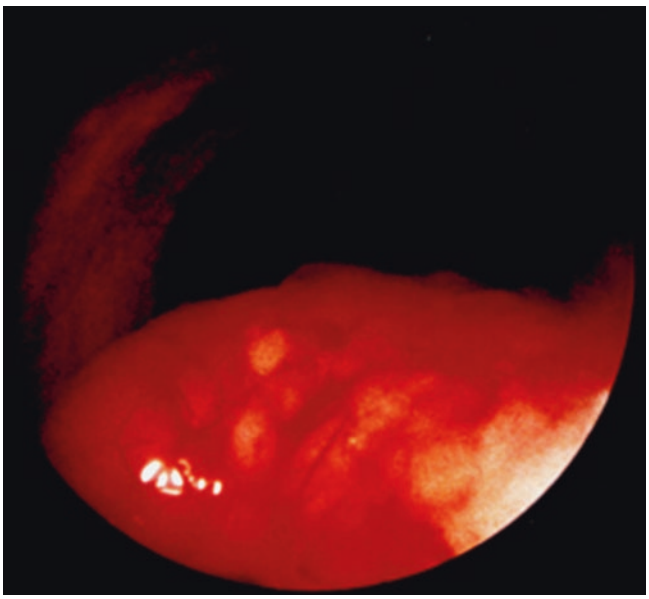

Fig. 14.9 Mucosa with exophytic proliferation with areas of congestion hemorrhage and a whitish tone in regions presenting more rapid growth, mammillated surface. Microhysteroscopic diagnosis: high-risk hyperplasia. HP: complex hyperplasia

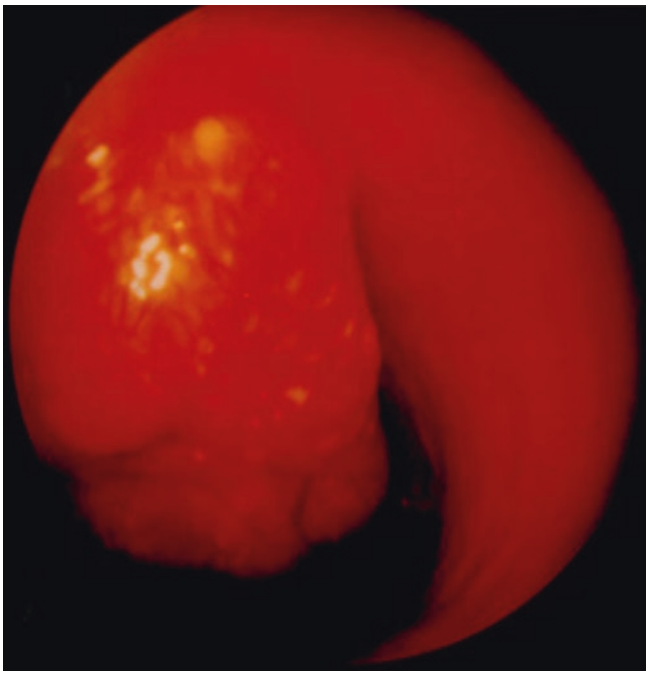

Fig. 14.10 Hysteroscopic image showing mucosal proliferation with greater vascularity. Hysteroscopic diagnosis: high-risk hyperplasia. Histopathologic diagnosis: atypical hyperplasia

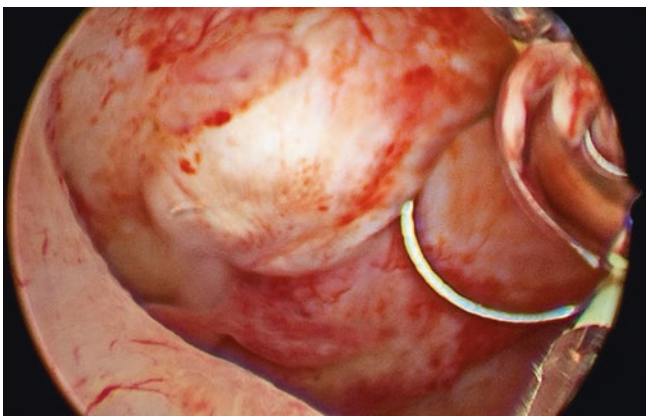

Fig. 14.11 Image: high-risk endometrial hyperplasia. Pathology: complex hyperplasia

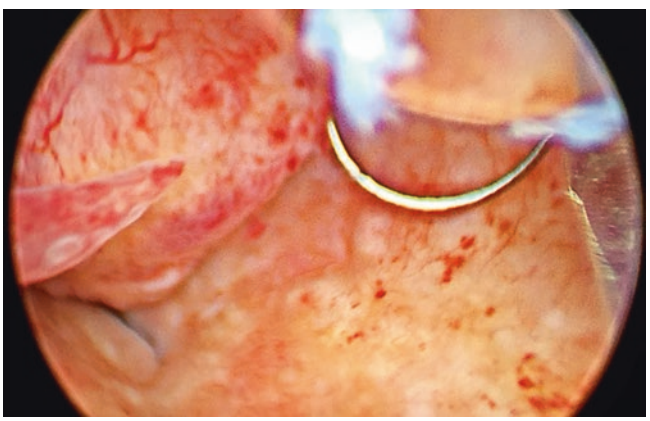

Fig. 14.12 Image: high-risk endometrial hyperplasia. Pathology: complex hyperplasia

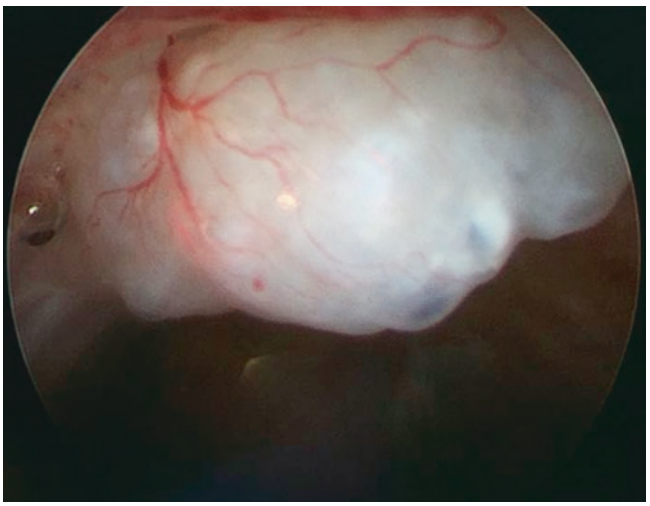

Fig. 14.13 Image: high-risk endometrial hyperplasia. Pathology: complex atypical hyperplasia

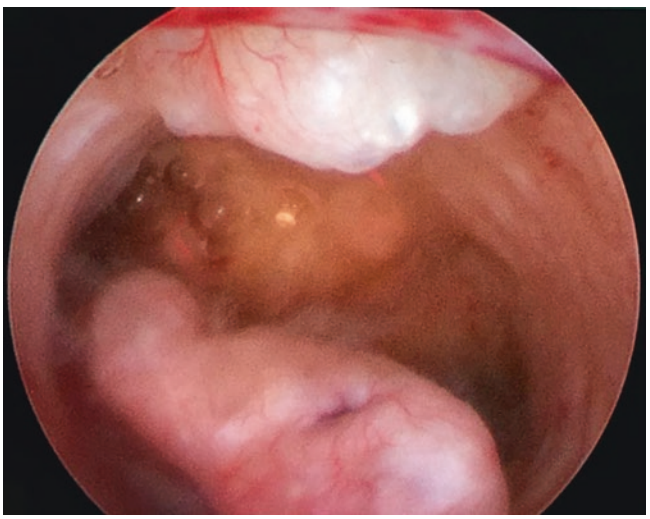

Fig. 14.14 Image: high-risk endometrial hyperplasia. Pathology: complex atypical hyperplasia

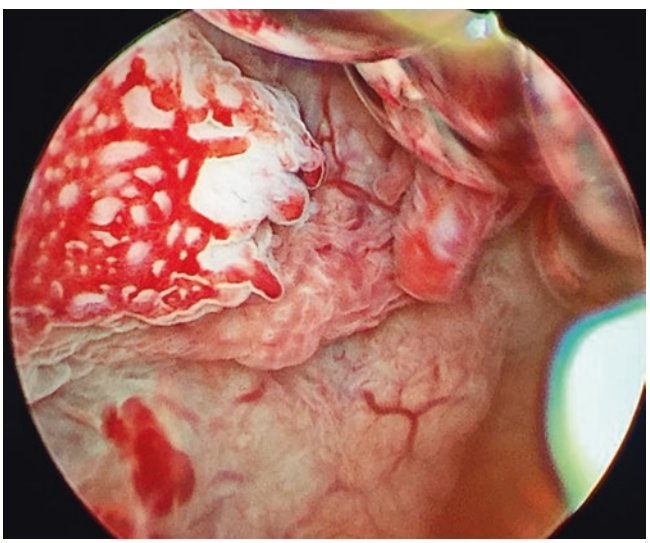

Fig. 14.15 Image: high-risk endometrial hyperplasia. Pathology: complex atypical hyperplasia

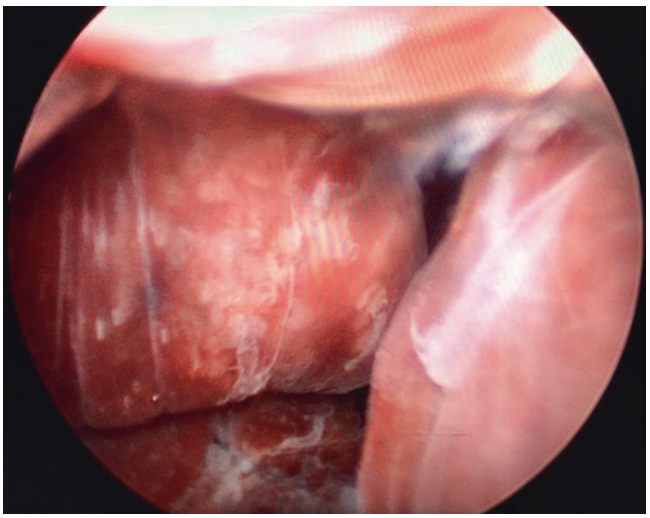

Fig. 14.16 Image: high-risk endometrial hyperplasia. Pathology: complex hyperplasia

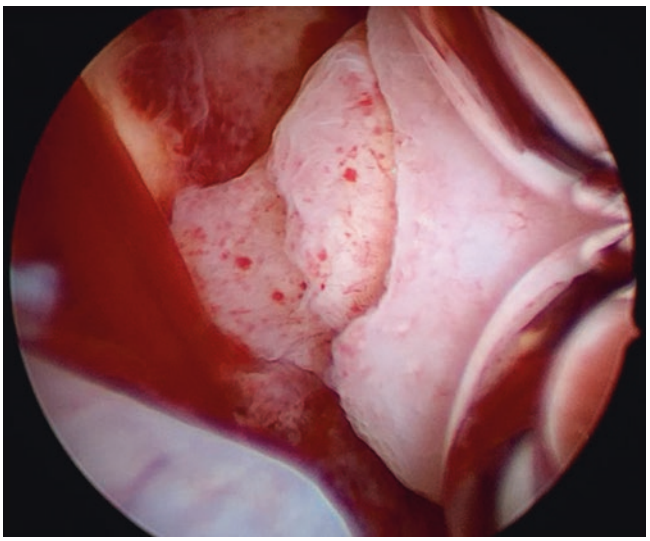

Fig. 14.17 Image: high-risk endometrial hyperplasia. Pathology: complex hyperplasia

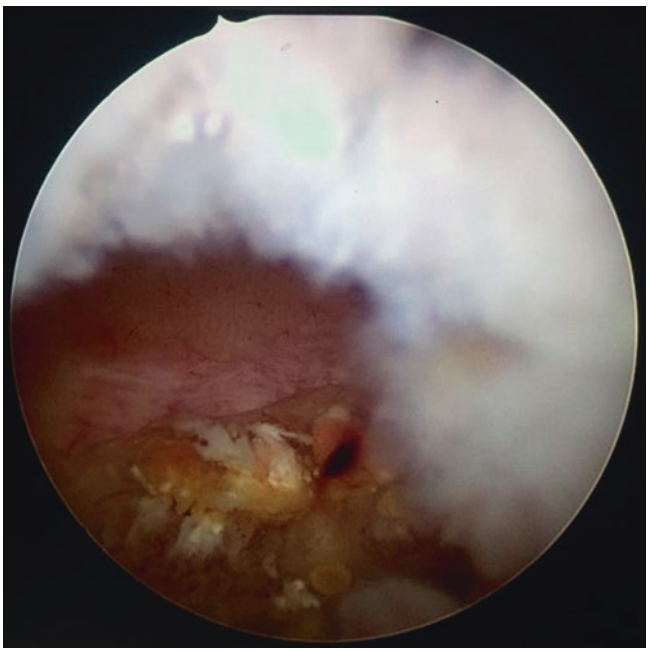

Fig. 14.18 Image: HRH. Pathology: atypical hyperplasia and carcinoma

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Endometrial Cancer

15

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15.1 Epidemiology

Endometrial carcinoma (EC) is the fourth most common cancer in women. It is defined as a gynecologic malignancy that arises from the endometrium, the inner uterine layer, and occurs above the level of internal cervical os involving the upper two-thirds of uterus (Fig. 15.1).

It is the most frequent cancer of the female genital tract in developed countries and represents 95% of uterine malignancies [1]. Its incidence is steadily rising and for example in the United States alone it has increased from 40,320 new cases in 2004 to about 54,870 new cases in 2015 [2, 3]. More than 70% of cases of EC are stage I at the time of diagnosis, when the reported 5-year survival rate is 90% [4].

The main age of diagnosis of EC is between the sixth decade and seventh one, with more than 90% occurring after 50 years of age. Approximately only 20% of EC are diagnosed in premenopausal age and among these about 5% of cases are represented by women under 40 years of age.

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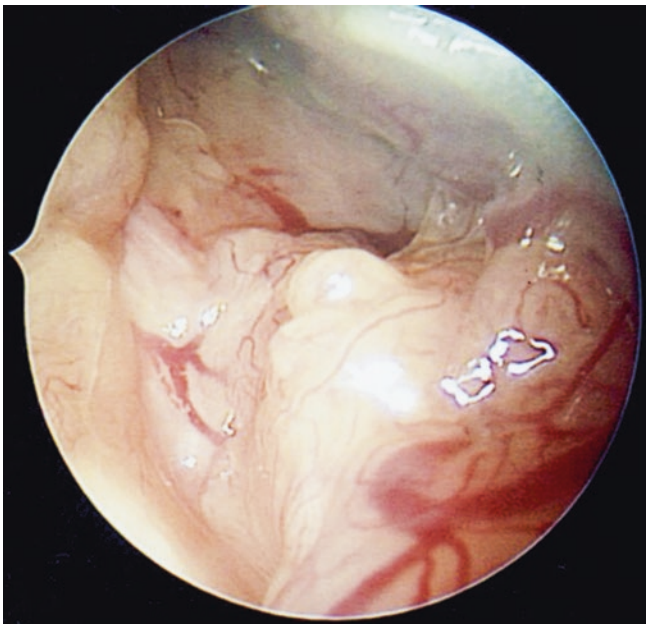

Fig. 15.1 Uterine cavity completely involved by mildly differentiated G2 endometrioid adenocarcinoma

15.2 Classification and Histopathology

Historically, EC has been classified into two main types that differ in epidemiology, genetics, prognosis, and even treatment:

- Type I, or endometrioid adenocarcinoma, which is the most common histologic type and is diagnosed in more than three-fourths of all cases (Figs. 15.2, 15.3, and 15.4)
- Type II, or non-endometrioid adenocarcinoma, which includes different subtypes as serous, clear cell, and undifferentiated carcinomas, as well as carcinosarcoma/malignant mixed Müllerian tumor [5]

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_15

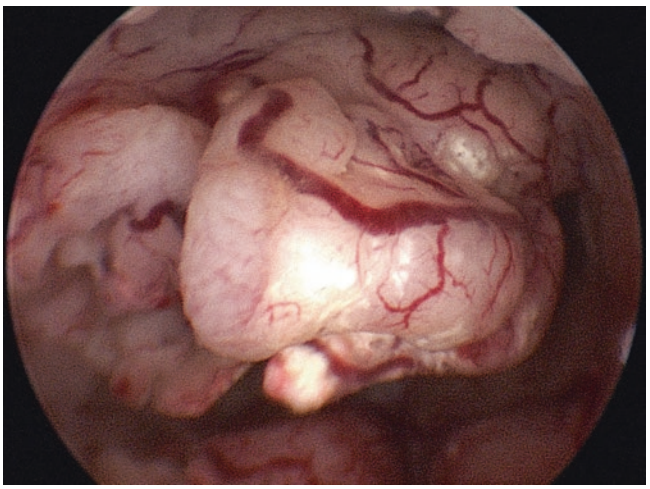

Fig. 15.2 Image of multilobular exophytic endometrial cancer with atypical pattern of vascularization (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

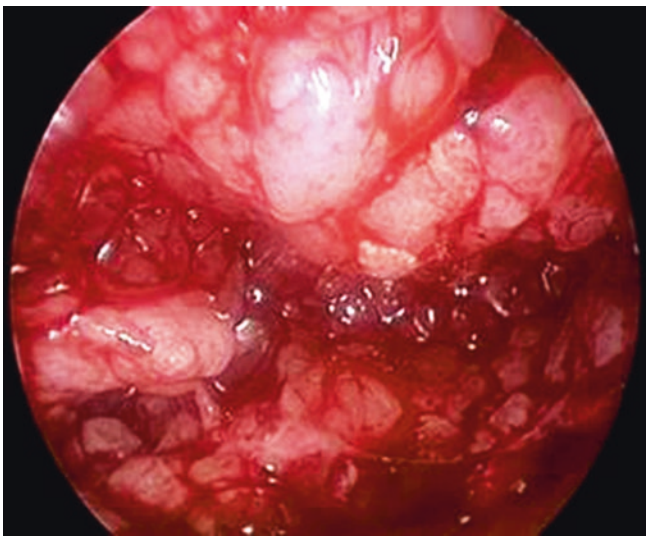

Fig. 15.3 Poorly differentiated G3 endometrial endometrioid cancer invading the uterine cavity

Type I tumors are tipically of low grade, diagnosed at early stage with the only involvement of uterus (Fig. 15.5). They are associated with exposure to unopposed estrogens from either internal or external sources. Thus, all the factors causing women's exposure to high levels of estrogen are associated with an increased risk of type I endometrial cancer. Similarly, also factors responsible for decreasing the levels of progesterone are linked with a greater risk of EC. Among the most commonly identified risk factors for type I endometrial cancer there are obesity, estrogen replacement therapy, nulliparity, medical conditions that result in high estrogen levels such as estrogen-secreting ovarian tumors, hormone therapy such as tamoxifen, hyperinsulinemia, type II diabetes, and polycystic ovarian syndrome [6–8].

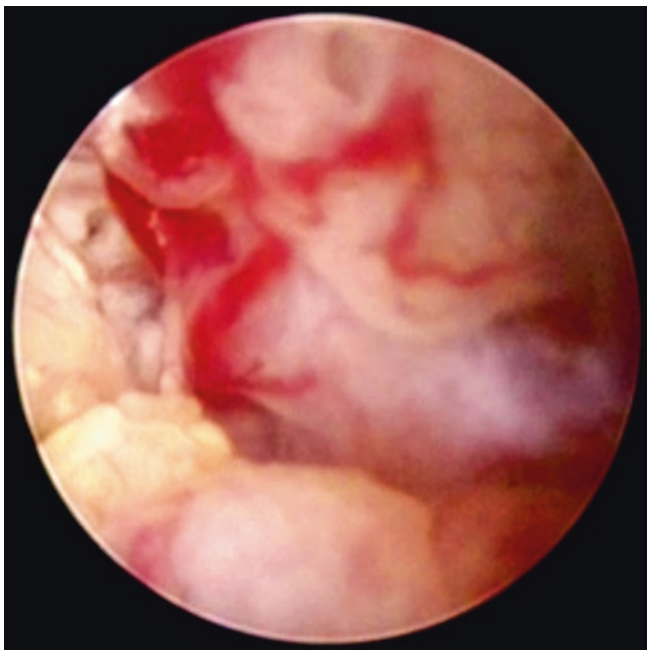

Fig. 15.4 Irregular vascular pattern with angiogenesis phenomenon in mildly differentiated G2 endometrioid endometrial cancer

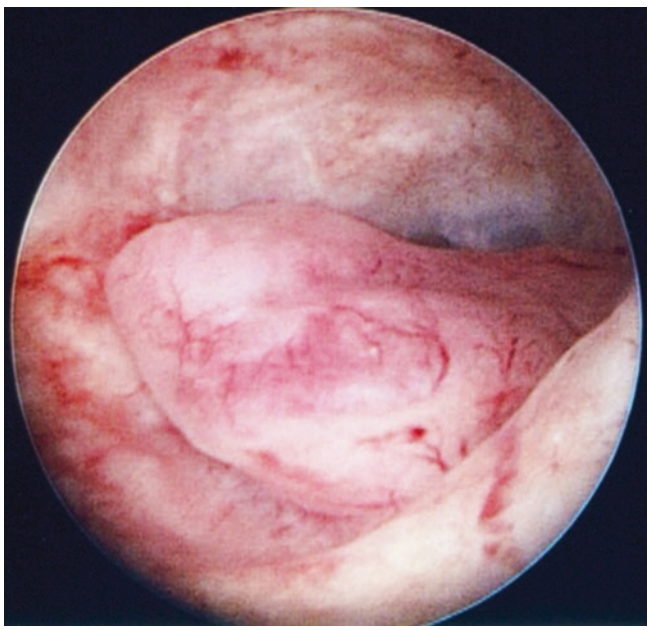

Fig. 15.5 Fibrocystic glandular polyp and arborescent vascularization with high risk for endometrial cancer (well-differentiated G1 endometrioid adenocarcinoma at histologic diagnosis)

Moreover, the endometrioid adenocarcinoma is more common than type II carcinoma in pre- and perimenopausal women and it has a good prognosis, with a 5-year overall survival rate which ranges from 75% to 86% [9]. The precursor lesion of type I endometrioid adenocarcinoma is endometrial intraepithelial neoplasia (also known as atypical endometrial hyperplasia) (Fig. 15.6).

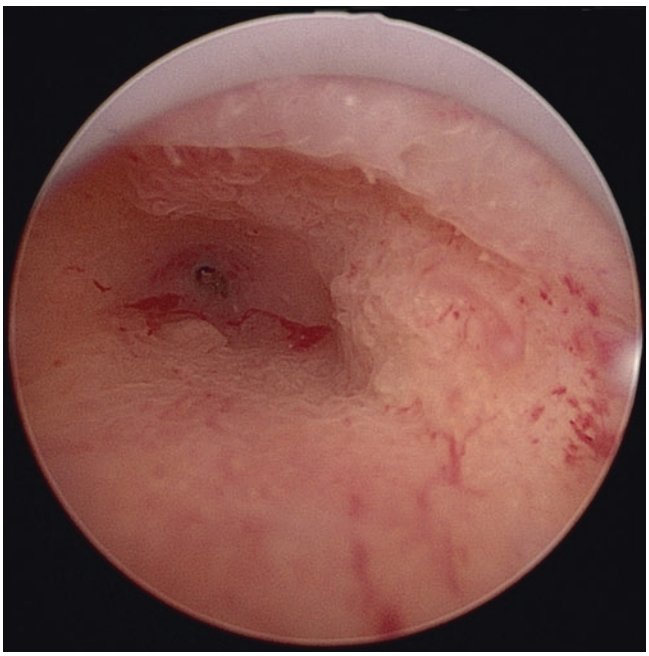

Fig. 15.6 Increased endometrial thickness in EIN

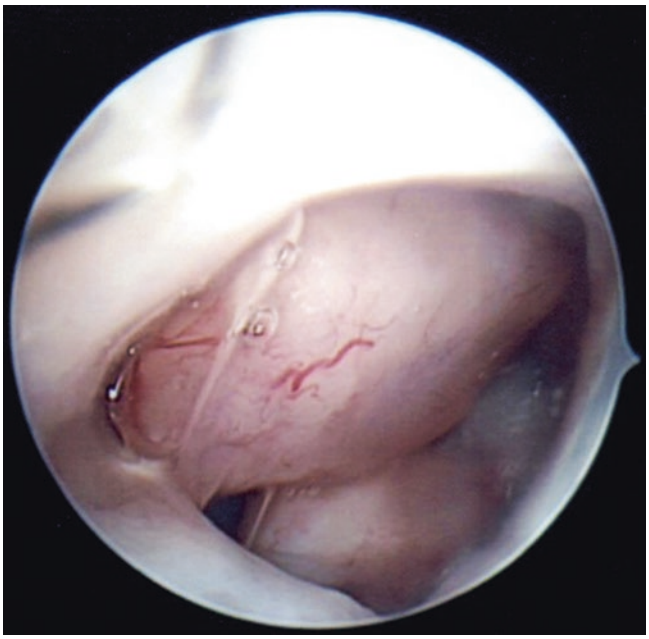

Fig. 15.7 EIC in sessile pseudo-polypoid formations and slightly increased vascularization

Actually there are two different systems of endometrial precancer nomenclature in common usage [9]:

1. The World Health Organization 1994 schema, based on two criteria, glandular complexity and nuclear atypia, used to distinguish four classes: simple (SH), complex (CH), simple atypical (SAH), and complex atypical hyperplasia (CAH), which have different progression risks of <1%, 3%, 8%, and 29%, respectively
2. The Endometrial Intraepithelial Neoplasia (EIN) diagnostic schema developed by the International Endometrial Collaborative Group in 2000, composed by three different classes (benign hyperplasia, endometrial intraepithelial neoplasia, cancer), which are defined in morphological, clinical, and biological terms [10]

The last classification seems to be preferable to the first one. The diagnosis of premalignant lesions should use criteria and terminology that clearly distinguish between clinicopathologic entities that are managed differently at present, and the EIN schema is tailored most closely to this target. The preferred terminology to define precancerous behavior is "endometrial intraepithelial neoplasia" rather than "atypical endometrial hyperplasia" [11].

When EIN is absent, the risk of progression to endometrioid carcinoma ranges from 1% to 8%, depending on the degree of architectural complexity. Instead the presence of endometrial intraepithelial neoplasia is associated with a greater likelihood of evolving into cancer. Moreover EIN may coexist with an undiagnosed EC in 30–50% of cases [12].

Type II tumors are estrogen-independent malignancies, usually developing from atrophic endometrial tissues, and in most cases they affect elderly women who are neither obese nor diabetic. A lot of studies suggested more aggressive course and worse prognosis even in early stages: only 35% of patients survive 5 years from diagnosis.

Uterine papillary serous carcinoma represents only 10% of all cases of uterine cancer, but it is responsible for the death of almost 40% of patients with EC [13]. Actually endometrial intraepithelial carcinoma is considered to be the precursor lesion [14, 15] (Fig. 15.7). Serous endometrial intraepithelial carcinoma could be associated with an extrauterine neoplastic localization at the time of diagnosis with a greater risk of recurrence, spread, and eventual death [16]. As papillary serous carcinoma, the clear cell histology is rare but associated with a poor prognosis [17].

Finally carcinosarcoma, also known as malignant mixed müllerian tumor of the uterus, is another histologic cell type with a poor prognosis.

15.3 Clinical Presentation

Abnormal uterine bleeding (AUB) is the most common presenting symptom of EC. The postmenopausal bleeding is principally caused by endometrial atrophy, which is identified in 50% of patients, while EC is diagnosed in 7–14% of these cases of AUB. Thus all patients with postmenopausal bleeding should undergo evaluation for possibile EC. In case of premenopausal endometrial malignancy the main symptoms are heavy irregular menses and intermenstrual bleeding.

Patients with advanced disease may have symptoms similar to those seen with advanced ovarian cancer, such as abdominal or pelvic pain, bloating, abdominal distention, and change in bowel or bladder function.

15.4 Diagnosis

15.4.1 Ultrasonography

Evaluation of the endometrium is the key component in the diagnostic management of women suspected of endometrial cancer or precancerous endometrial lesion. There are no screening tests to detect EC in women with no symptoms. However abnormal uterine bleeding in post- and pre-menopause, above all in patients with risk factors, should always be assessed.

The investigative approach should be dictated by a specific order of diagnostic exams. The American College of Obstetricians and Gynecologist suggests transvaginal ultrasound as a possible first instrumental examination. It is currently the first-line evaluation tool for the patients with AUB. During this exam, the thickness of the endometrium and the size of the uterus are measured.

In postmenopausal women an endometrial thickness greater than 4 mm or not assessable should undergo further evaluation. Instead in younger women with signs and symptoms of AUB, risk factors and other medical factors should be considered to decide whether a biopsy is needed [11]. The literature is unclear about when evaluation with imaging is indicated in these patients, because the only ultrasound measurement of endometrial thickness in premenopausal women has no diagnostic value. Thus the decision to histologically evaluate the endometrium should be based on symptomatology and clinical presentation [11].

As rarely endometrial carcinoma (particularly type II) can occur with an endometrial thickness of less than 3 mm, persistent or recurrent uterine bleeding should prompt a histologic evaluation of the endometrium regardless of endometrial thickness.

15.4.2 Diagnostic Hysteroscopy

Classically, dilation and curettage (D&C) has been the main technique used to obtain a histologic diagnosis of EC. The development of new devices and techniques has made it possible to sample endometrium in an outpatient setting, replacing D&C performed in the operatory room.

Nowadays office hysteroscopy with biopsy is considered the gold standard for diagnostic evaluation of women with abnormal uterine bleeding, above all in patients with a higher risk of cancer [18]. It became popular, since it could be performed without anesthesia (Fig. 15.8).

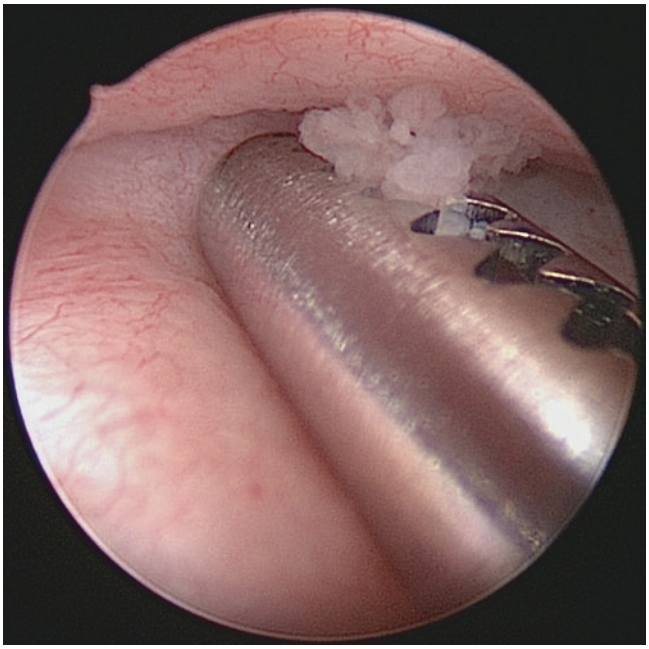

Fig. 15.8 Endometrial biopsy performed by 5-Fr cold instrument during office hysteroscopy. Endometrial lesion suspected for adenocarcinoma

Hysteroscopy is a minimally invasive procedure that, through a direct visualization of the uterine cavity, allows firstly an accurate study of endometrial surface and then to perform a tailored biopsy of suspicious areas during the same exam. Different studies have shown that it could be very useful in assessing focal lesions that may be missed with blind biopsies, as in case of D&C [19, 20] (Fig. 15.9).

The majority of authors agree that the accuracy of diagnostic hysteroscopy performed for endometrial lesions is good for diagnosis of clearly malignant pathologies (Figs. 15.10 and 15.11), but it is only moderate for endometrial hyperplasia [21, 22].

Some morphological criteria have been used as hysteroscopic predictors of endometrial hyperplasia throughout the years, but they have not been defined based on scientific evidence. Moreover there is no agreement in literature about these parameters. Despite several studies aimed to standardize the hysteroscopic description of endometrial carcinoma and hyperplasia, none have established a standardized morphological schema to distinguish these lesions in a statistically significant way.

Ianeri at al. have proposed a new hysteroscopic morphological scoring system, based on eight morphological variables with a statistical significance (Figs. 15.12 and 15.13). Allocating a score to each variable, they have identified four different intervals corresponding to four categories (normal endometrium, endometrial hyperplasia without atypia, complex atypical endometrial hyperplasia, adenocarcinoma) [23]. This scoring system has showed

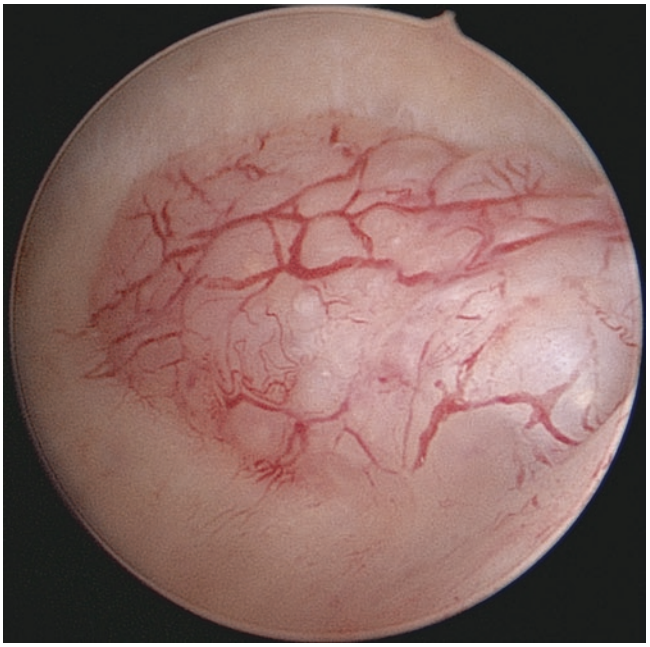

Fig. 15.9 Sessile cystic polyp of the posterior uterine wall and increased capillary vascularization

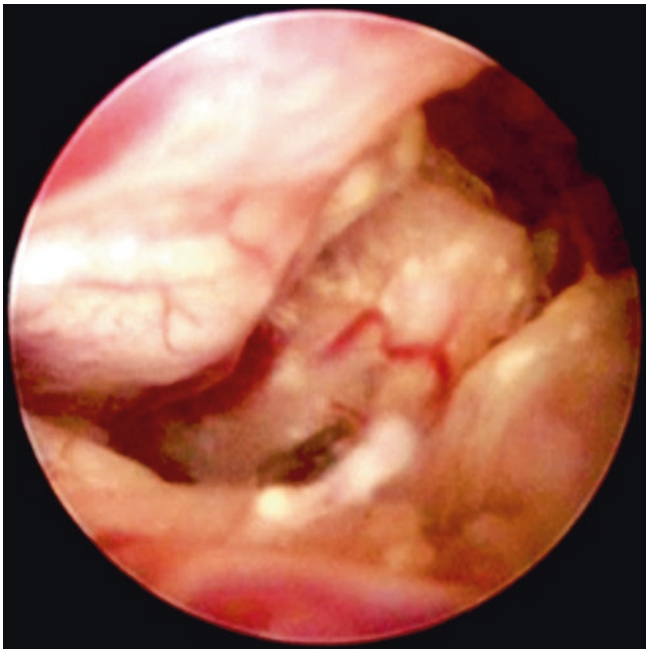

Fig. 15.11 Crumbly whitish exophytic lesion involving the entire uterine cavity

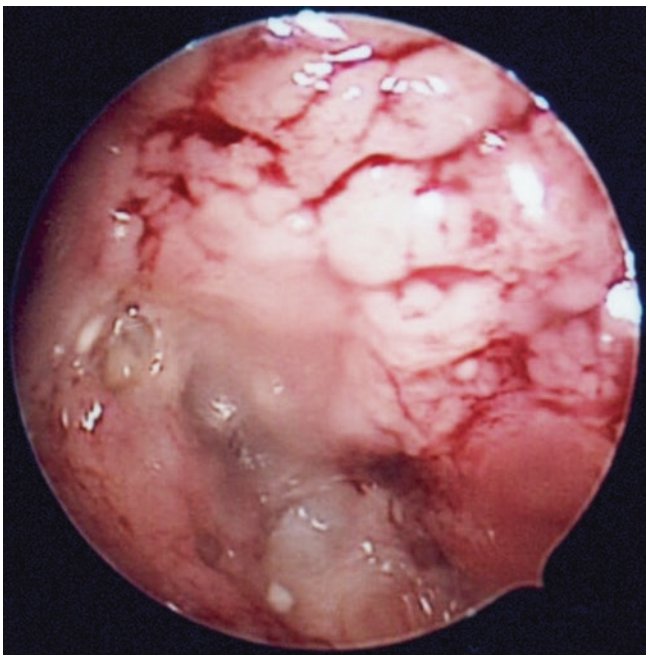

Fig. 15.10 Endometrial mildly differentiated G2 cancer involving the anterior and right walls of the uterus. "Cerebroid endometrial pattern" and vascular ectasia

Fig. 15.12 Vascular ectasia in mildly differentiated G2 endometrioid adenocarcinoma

good diagnostic performance, in particular regarding endometrial cancer and less regarding endometrial hyperplasia. Moreover, according to this diagnostic system the classification of endometrial lesions is based on a total score, which can be confusing and tedious. Thus, other new studies are necessary to improve the proposal of Ianeri et al. elaborating a more precise standardized risk classification with a scoring system that could assist, in particular the

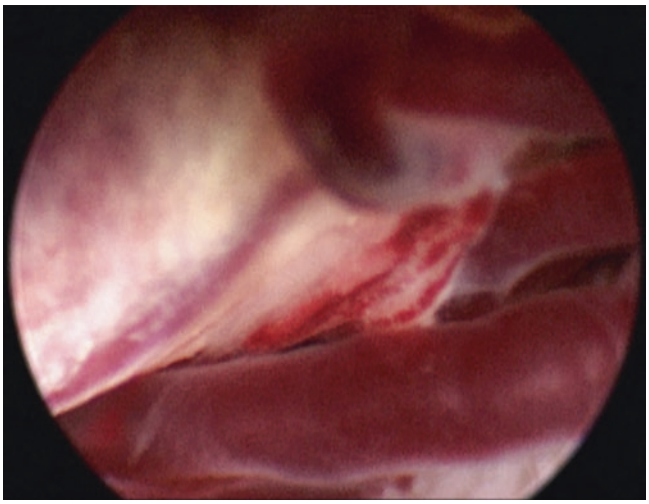

Fig. 15.13 Hysteroscopic image of bridge vessels (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

less experienced operators, in the differential diagnosis among normal endometrium, endometrial hyperplasia, and endometrial carcinoma.

Nevertheless using the morphological patterns described by Ianieri et al., the different endometrial hysteroscopic appearances can be classified into the following classes:

1. Normal endometrium
2. Low-risk endometrial hyperplasia
3. High-risk endometrial hyperplasia
4. Endometrial cancer
5. Atypical endometrial pattern of undetermined significance

15.4.2.1 Normal Endometrium

The uterine cavity appears covered by a flat endometrium, with clear, regular arrangement of the glandular ostia and regular vascularization (Fig. 15.14).

15.4.2.2 Low-Risk Endometrial Hyperplasia

This includes proliferative disorders of endometrium, endometrial polyps, and hyperplasia without atypia. The hysteroscopic appearance includes:

- Increased endometrial thickness
- Nonhomogeneous endometrial regeneration (Fig. 15.15)
- Widened glandular ostia (Fig. 15.16)
- Irregular arrangement of the glandular ostia (Fig. 15.17)
- Polypoid formations (Figs. 15.18, 15.19, 15.20, and 15.21)
- Presence of ciliated epithelium
- Presence of cystic dilatation (Figs. 15.22a,b and 15.23)

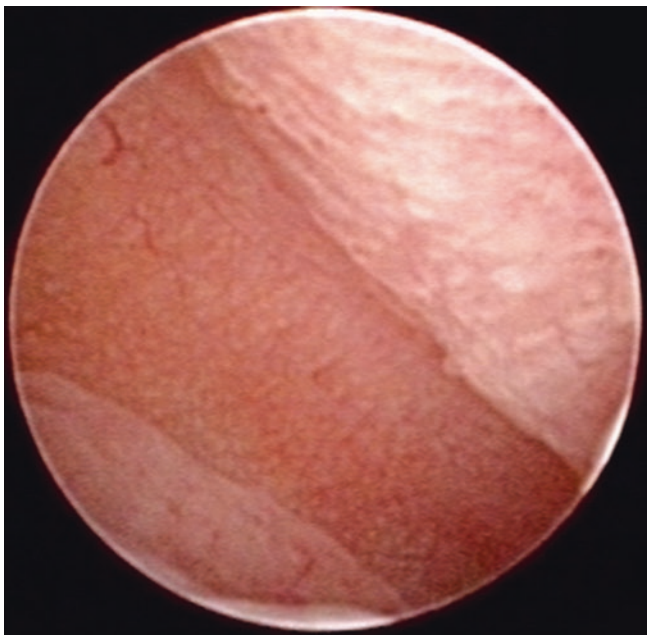

Fig. 15.14 Regular arrangement of the glandular ostia in fundal area (white spots) (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

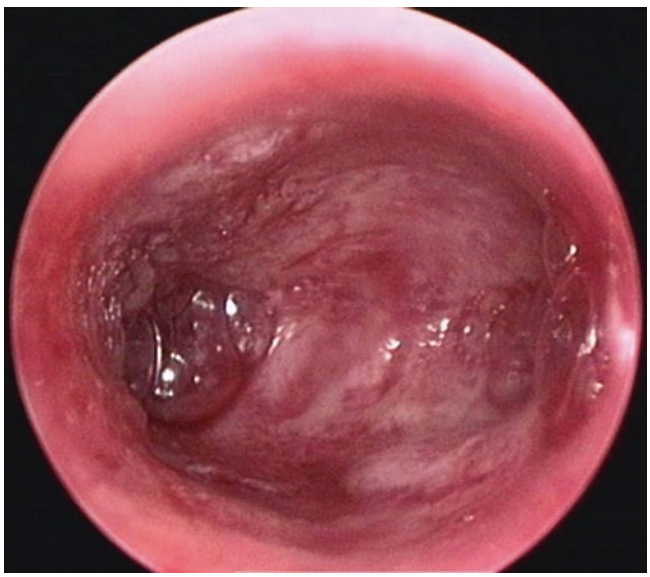

Fig. 15.15 Focal endometrial thickening surrounded by atrophic endometrium

- Increased vascularization (Figs. 15.24 and 15.25)

If one or more of these features are found, hyperplasia must be suspected and a tailored biopsy should be performed (Fig. 15.26).

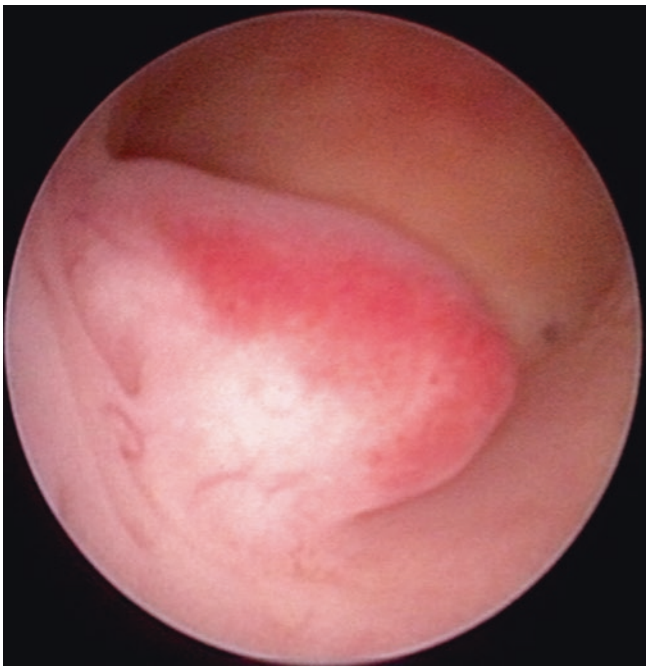

Fig. 15.16 Endometrial polyp with widened glandular ostia, with background endometrium in proliferative phase (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

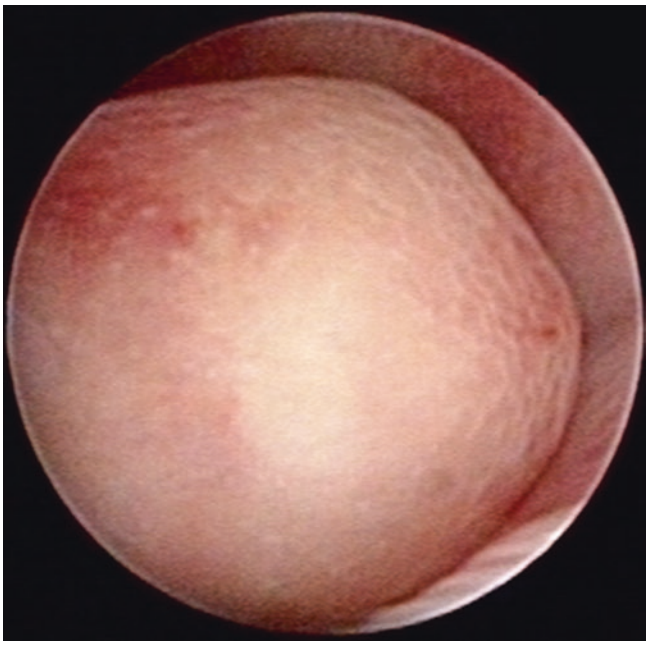

Fig. 15.18 Endometrial polyp: a pink polypoid endometrial change in low-risk endometrial neoplasia mass (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

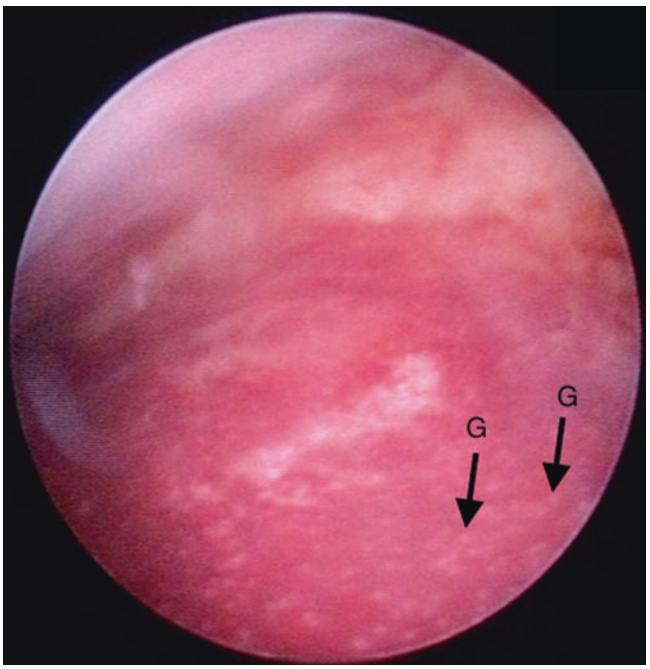

Fig. 15.17 Each G (arrow) represents an ostium. Irregular arrangement of the glandular ostia is seen on the polypoid mass (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

Fig. 15.19 Sessile endometrial polyp arising from the uterine fundus surrounded by atrophic endometrium

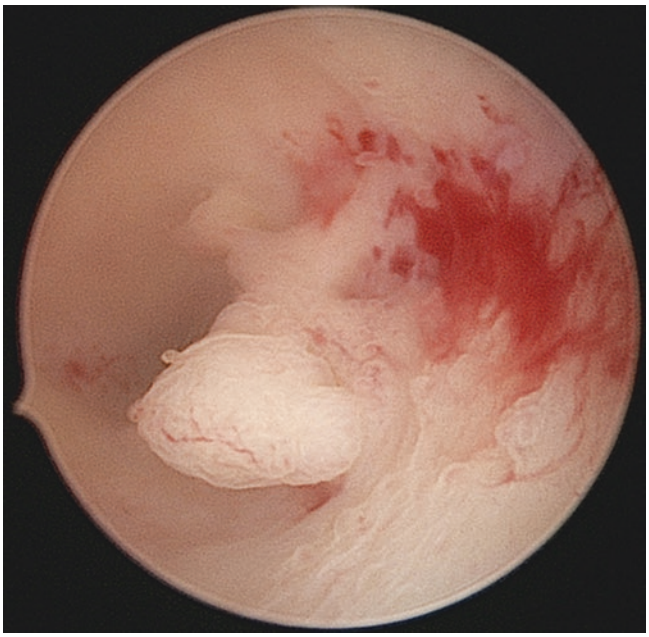

Fig. 15.20 Crumbly endometrial polypoid formation with irregular surface and slightly increased vascularization

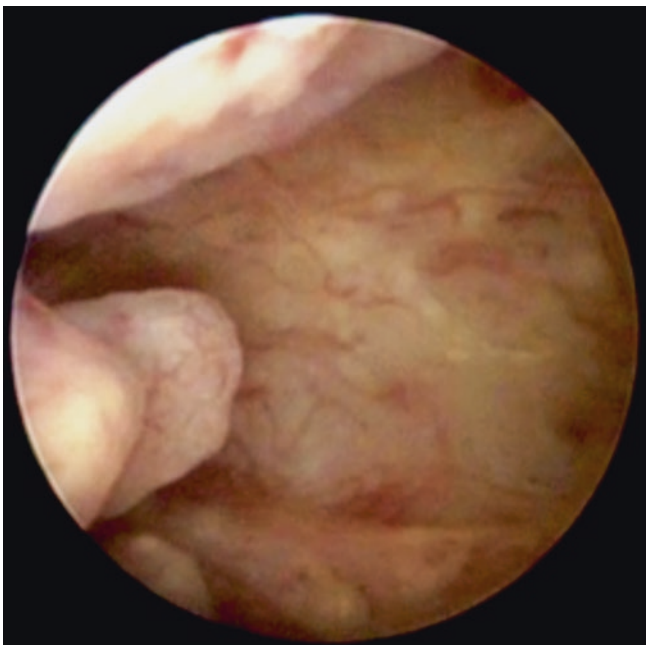

Fig. 15.21 Endometrial atypical polyps surrounded by atrophic endometrium

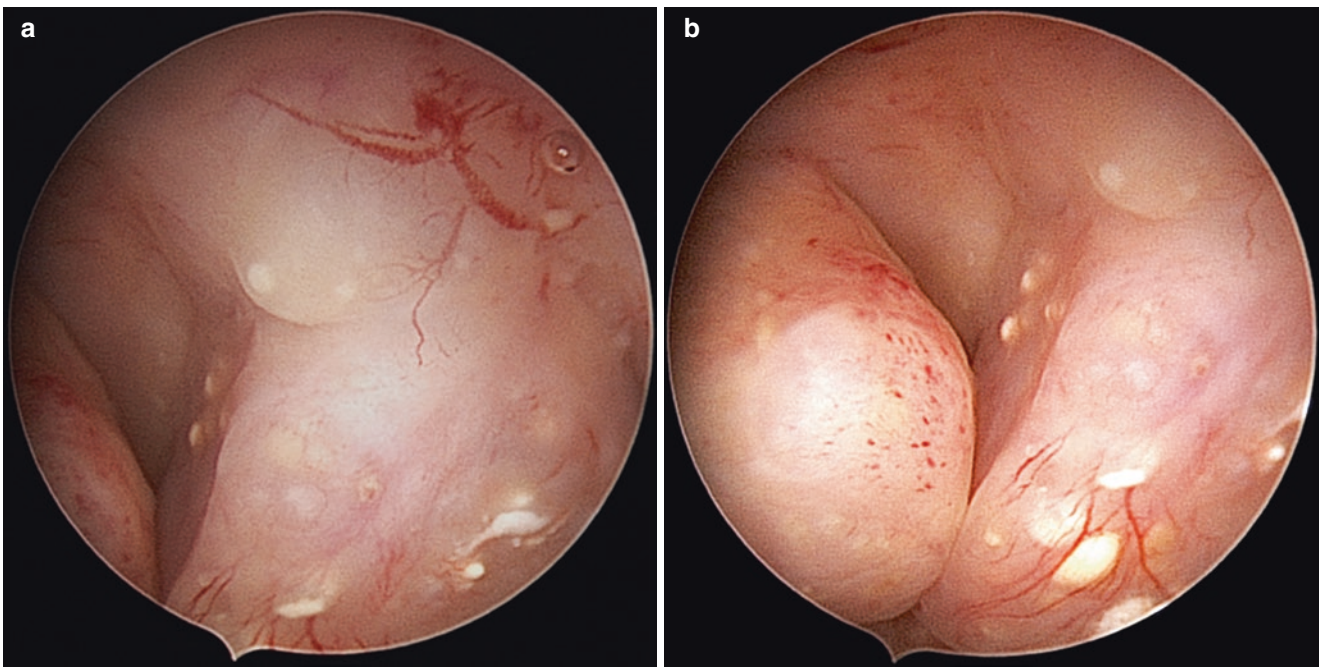

Fig. 15.22 (**a**, **b**) Endometrial polypoid hyperplasia areas of cystic degeneration and increased vascularization

Owing to the plasticity of the mucosa, its thickness can be assessed by palpation using the tip of the hysteroscope. The cystic endometrium is included in this group and it is characterized by widened glandular ostia with cystic–glandular formations of approximately 1 mm in diameter (Fig. 15.27). The same findings can be observed in a thinner endometrium indicating a condition of cystic atrophy.

15.4.2.3 High-Risk Endometrial Hyperplasia

This group includes conditions with hysteroscopic aspects similar to preneoplastic or neoplastic lesions.

The hysteroscopic appearance resembles:

– Irregular shape of endometrial surface (Figs. 15.28, 15.29, and 15.30)

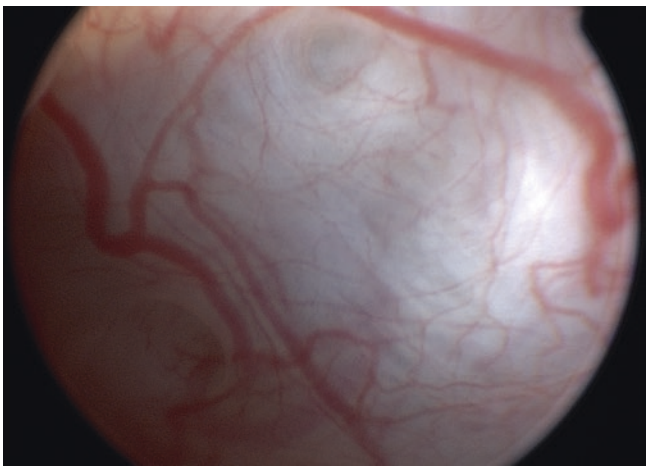

Fig. 15.23 Magnification of cystic glandular formation in endometrial cancer (Image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

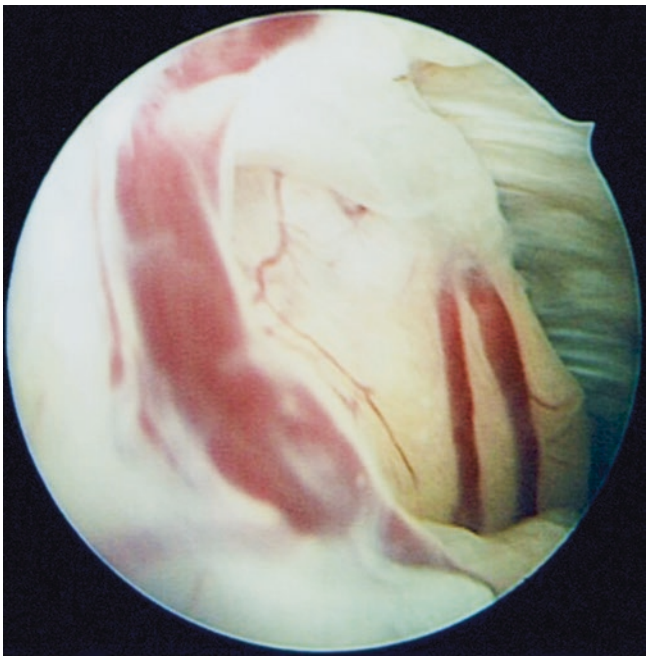

Fig. 15.24 Hysteroscopic image of vascular ectasia associated with angiogenesis phenomenon

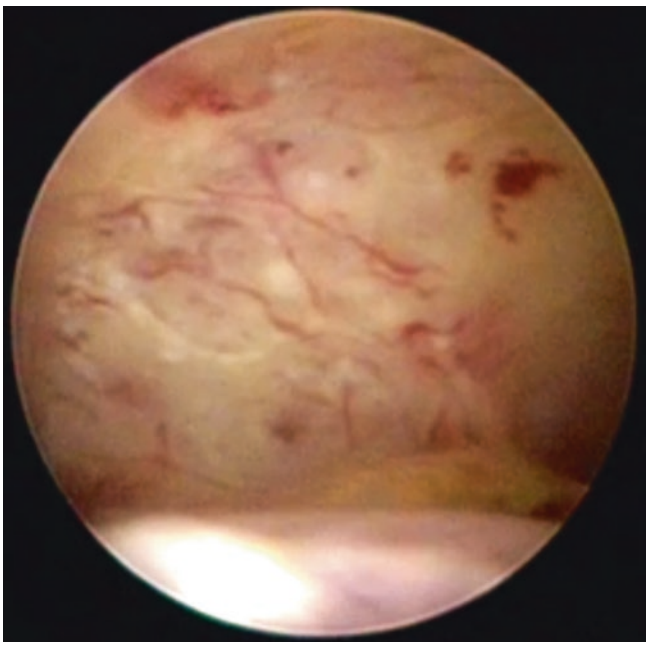

Fig. 15.25 Atrophic endometrium and increased vascularization

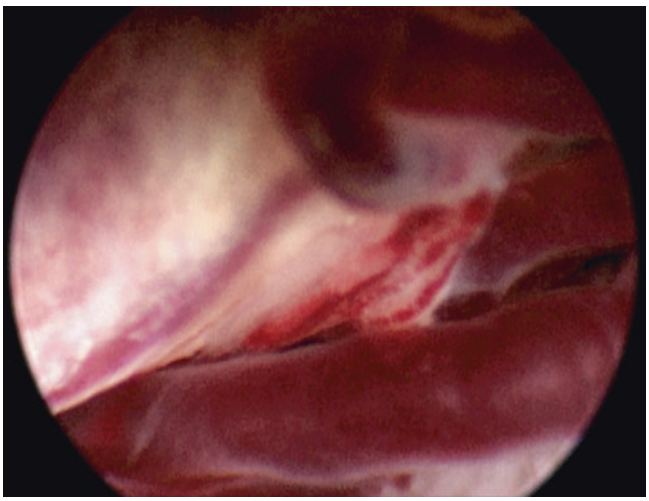

Fig. 15.26 Aberrant endometrial growth with cystic appearance and increased superficial vascularization (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

- Sharply angled polypoid change (Figs. 15.31, 15.32, and 15.33)
- Absent glandular ostia (Fig. 15.34)
- Abnormal vascularization (arborescent or corkscrew appearance) (Figs. 15.35, 15.36, 15.37, 15.38, 15.39, and 15.40)

High-risk endometrial hyperplasia suggests the probable presence of a precancerous lesion that has to be identified (Fig. 15.41, 15.42, 15.43, and 15.44).

Morphological description of this category is based on the pathological features of atypical hyperplasia, characterized by gland-to-stromal ratio greater than 1:1.

In this condition, glandular ostia are too close to each other to be distinguished during the hysteroscopic exam. The mucosal surface may appear torturous, irregularly shaped, or sharply angled, with abnormal vascularization (Figs. 15.45, 15.46, and 15.47).

15.4.2.4 Endometrial Cancer (EC)

The endoscopic images of EC are so clear and obvious to interpret that they are rarely confused with other lesions (Figs. 15.48 and 15.49).

Identify the hysteroscopic features essential for a hysteroscopist to increase the accuracy of this exam [21].

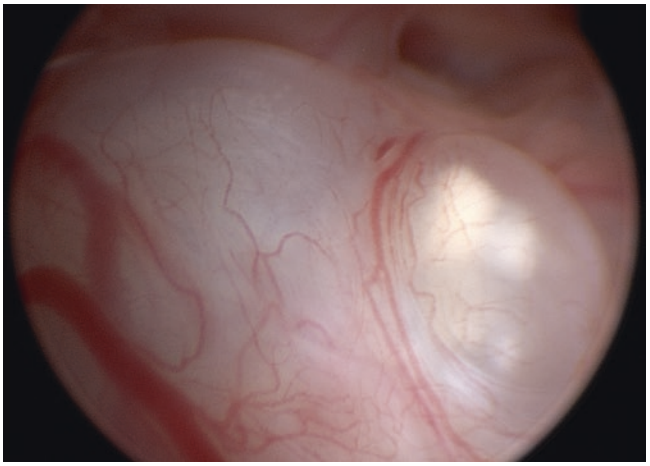

Fig. 15.27 Image of cystic endometrial degeneration (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

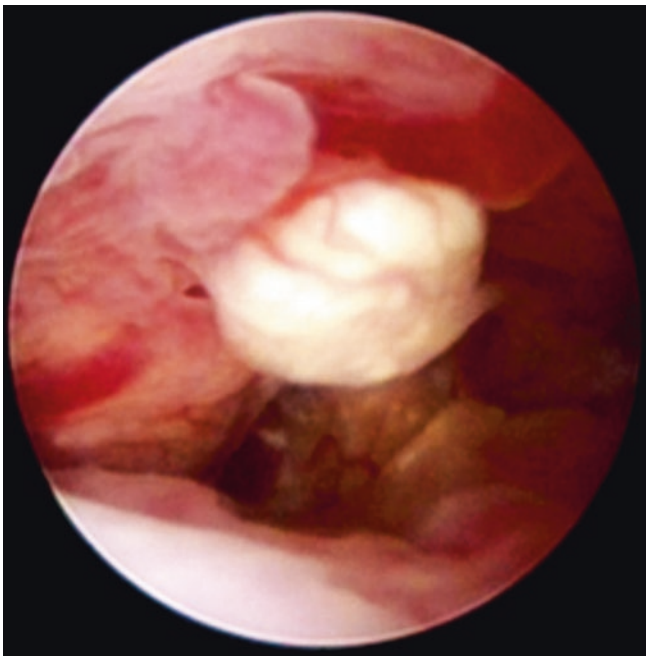

Fig. 15.28 Polypoid pattern of growth and aberrant vascularization

The following morphological aspects of endometrium are characteristic of EC:

- White or gray irregular and multilobular excrescences (Figs. 15.50 and 15.51)
- Necrotic or bleeding areas (Figs. 15.52 and 15.53)
- Crumbling of endometrial lesions (Fig. 15.54)
- Absent glandular ostia (Fig. 15.55)
- Cerebroid pattern (Figs. 15.56, 15.57, 15.58, and 15.59)
- Abnormal irregular vascularization with "glomerular pattern" (Figs. 15.60, 15.61, 15.62, 15.63, and 15.64)

Fig. 15.29 4 mm Polypoid endometrial area characterized by whitish "seaweed" surface and low compactness

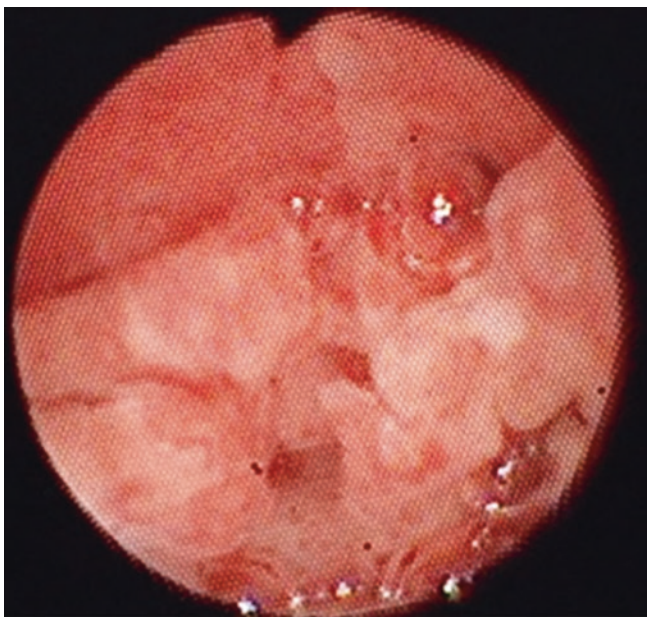

Fig. 15.30 Irregular shape of endometrial surface in atypical hyperplasia (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

These malignant lesions are often described as polypoid areas with an abnormal growth defined "cerebroid," because the surface is similar to the irregular superficial appearance of brain tissue [24] (Fig. 15.65). Moreover they are characterized by an irregular vascularization with a globular pattern similar to the renal glomerulus.

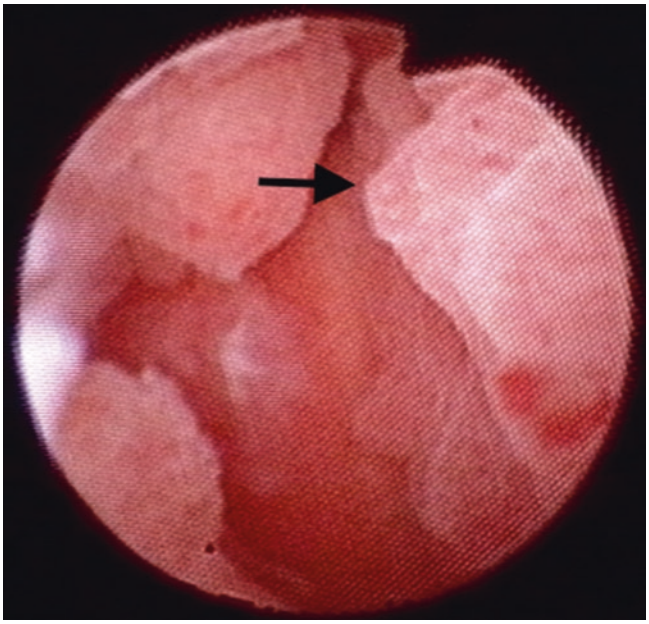

Fig. 15.31 Arrow points to sharply angled polypoid change in atypical hyperplasia (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

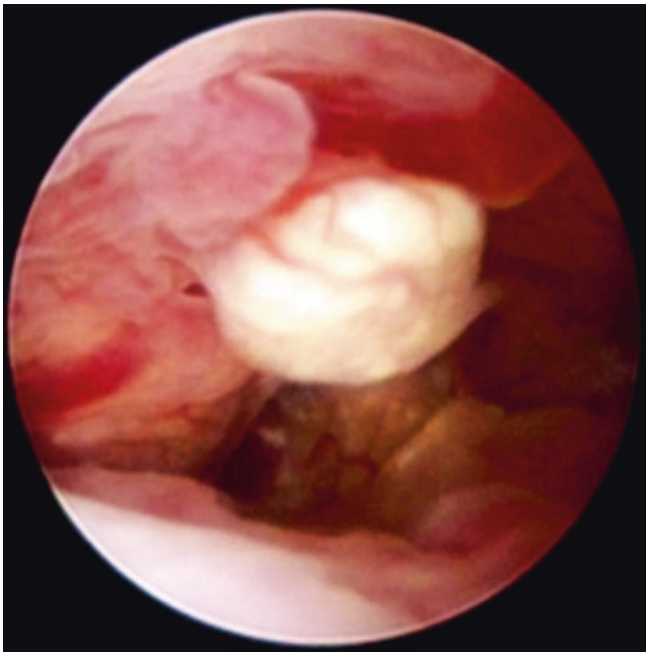

Fig. 15.33 Endometrial sessile polyp characterized by increased vascularization. Mildly differentiated G2 endometrioid adenocarcinoma

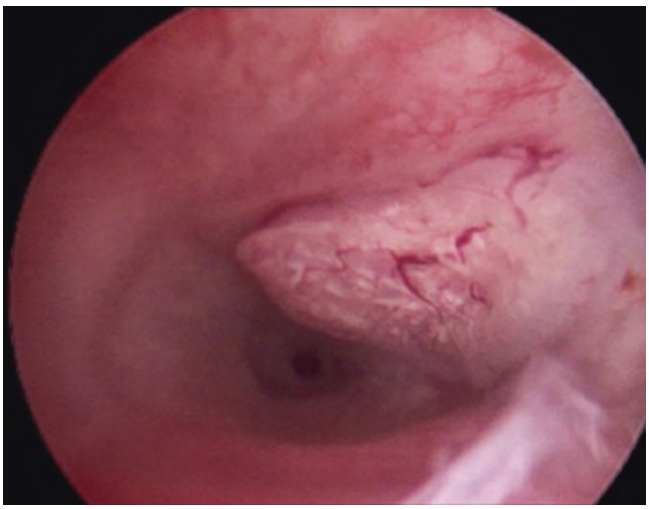

Fig. 15.32 Polypoid endometrial cancer in front of left tubal ostia (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

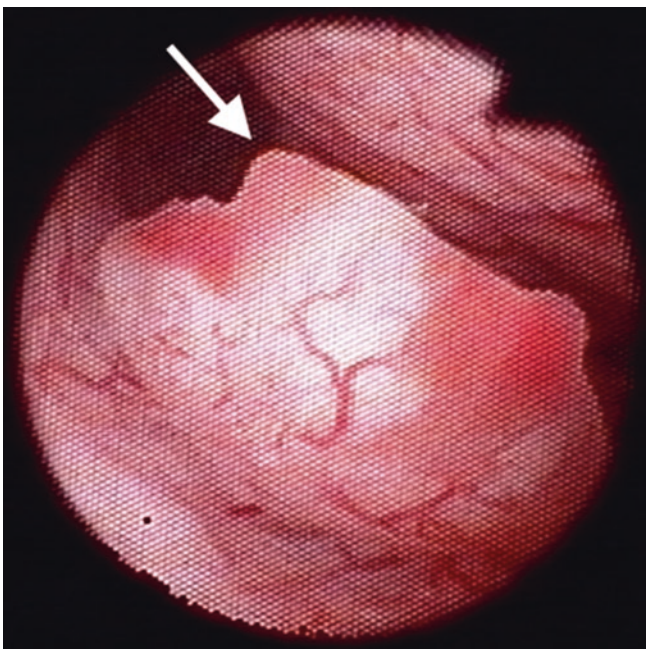

Fig. 15.34 Absent glandular ostia because of high gland-to-stromal ratio hyperplasia (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

Sometimes the malignant area can be clearly demarcated from the normal endometrium (Fig. 15.66); in other cases the lesion can be surrounded by a hyperplastic endometrial background with not well-defined edges (Figs. 15.67 and 15.68).

15.4.2.5 Atypical Endometrial Pattern of Undetermined Significance

This category consists of all features that cannot be precisely classified, but have atypical characteristics (Figs. 15.69 and 15.70).

15.4.3 Office Hysteroscopy

In patients with AUB and the suspect of uterine intracavitary pathology, hysteroscopy is considered to be the gold standard. The office hysteroscopy must be considered as an

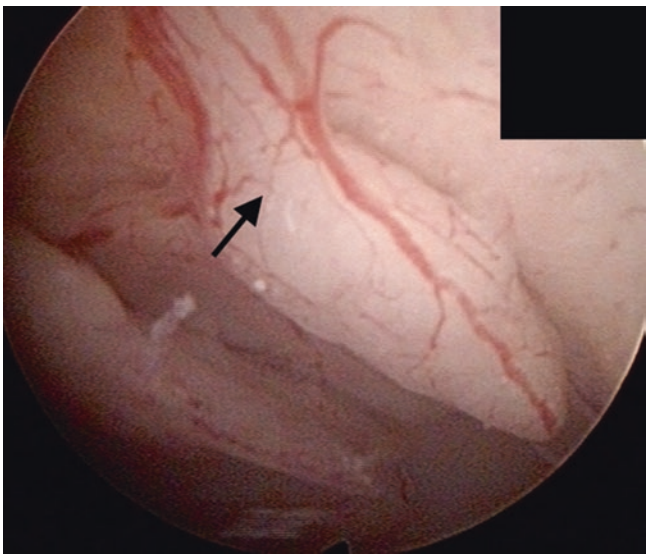

Fig. 15.35 Arrow points to vascularization change with bridged formations between two vesicular branches in grade 1 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

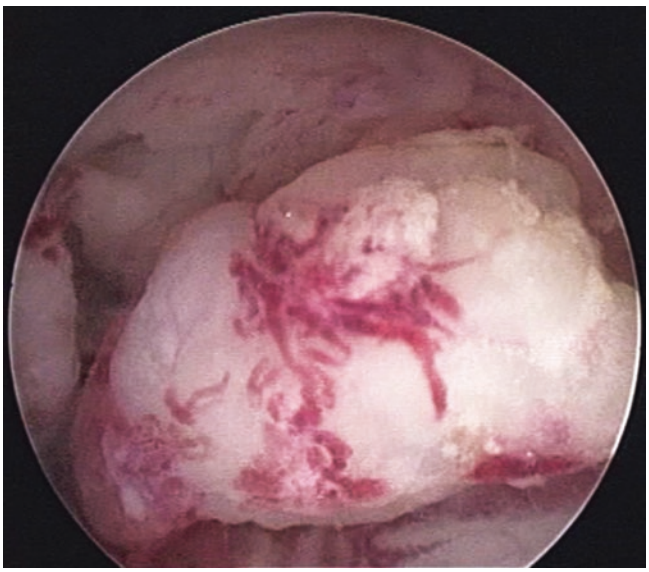

Fig. 15.37 Widespread endometrial cancer with crumbly polypoid formations and areas of increased angiogenesis (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

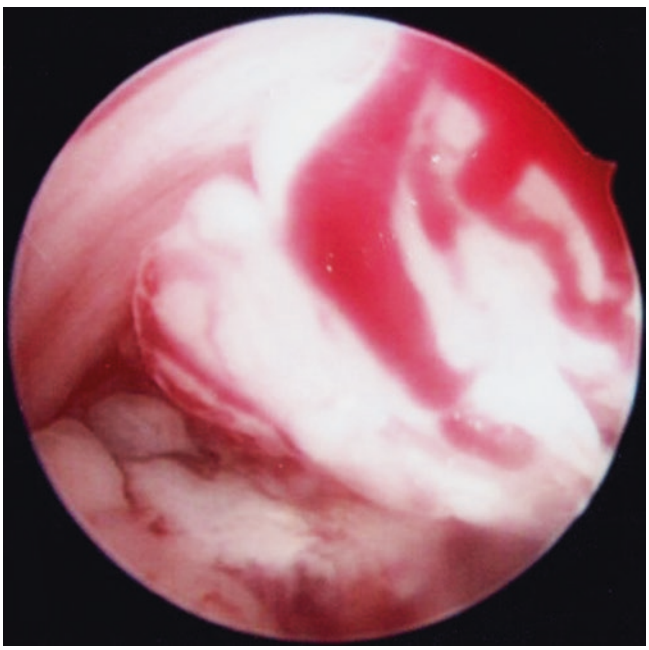

Fig. 15.36 Crumbly endometrial polypoid lesion characterized by irregular surface with vascular ectasia

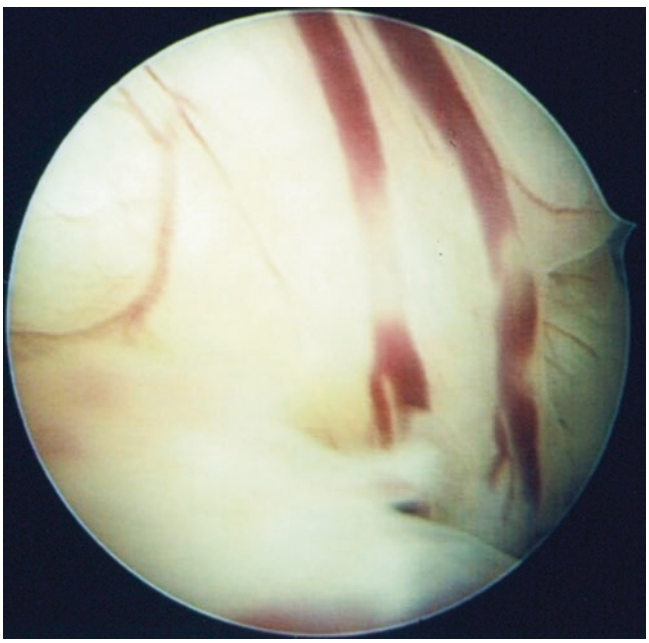

Fig. 15.38 Focal well-differentiated G1 endometrioid adenocarcinoma in polypoid endometrium with vascular ectasia

investigative method that has to be combined with endometrial eye-guided tailored biopsy to obtain a correct histologic diagnosis. It is necessary to identify benign or malignant lesions of endometrium for which a targeted biopsy is required (Figs. 15.71 and 15.72).

The diagnostic accuracy of hysteroscopy without tissue biopsy depends on the endoscopist's experience. In their study De Marchi at al. showed that diagnostic hysteroscopy made by residents had 60%, 9.09%, and 70.4% sensitivity (SE) and 97.1%, 98.8%, and 99.1% specificity (SP) in detecting hyperplasia without atypia, hyperplasia with atypia, and endometrial cancer, respectively. On the other hand, the instrumental exam made by seniors resulted in 85%, 72.7%, and 96.3% SE and 99.8%, 99.8%, and 100% SP, in detecting the same three histological findings [25].

Thus the hysteroscopist's experience is very important to well recognize premalignant and malignant lesions.

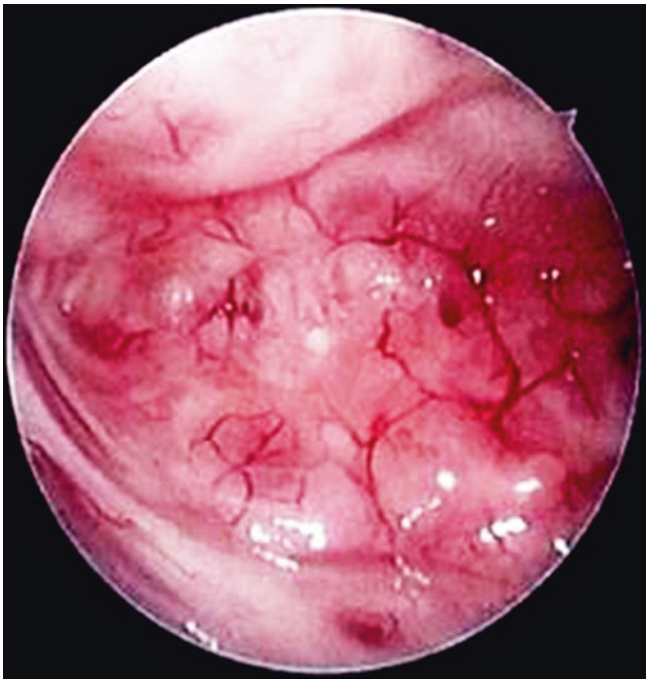

Fig. 15.39 Endometrioid cancer and irregular surface with abnormal vascularization

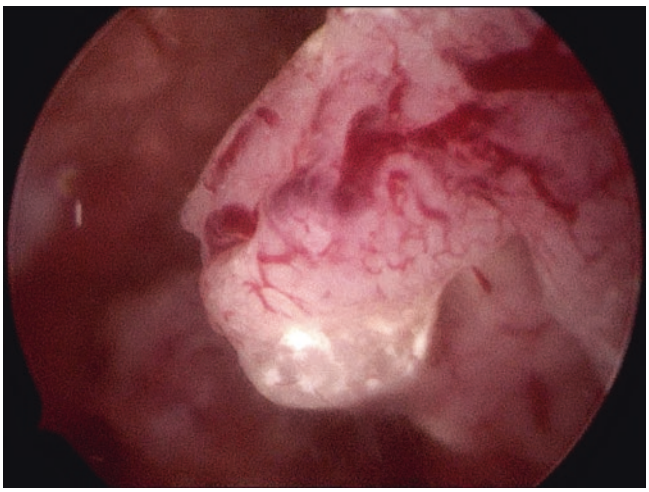

Fig. 15.40 Angiogenesis phenomenon in exophytic endometrial cancer (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

The office hysteroscopy with tailored endometrial sampling increases the accuracy of diagnosis of preneoplastic and neoplastic forms up to 100%.

The main advantages of office hysteroscopy with biopsy include the following:

- No need of cervical dilation.
- No need of general or spinal anesthesia; in some cases local analgesia can be used.

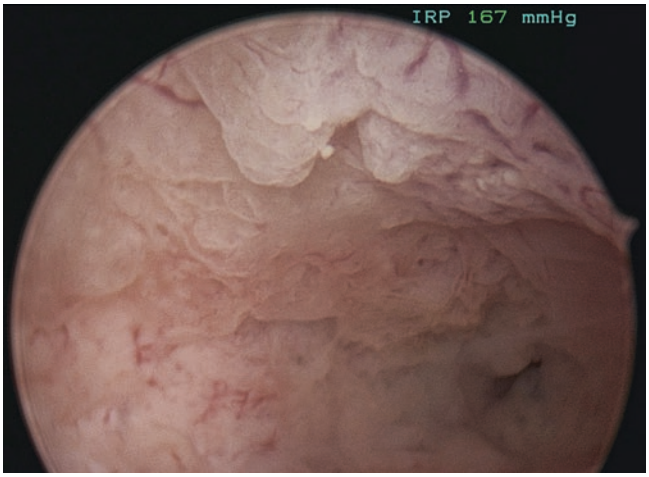

Fig. 15.41 Widespread abnormal endometrial polypoid growth (image supplied by A. Di Spiezio Sardo, Md, PhD, University of Federico II, Naples, Italy)

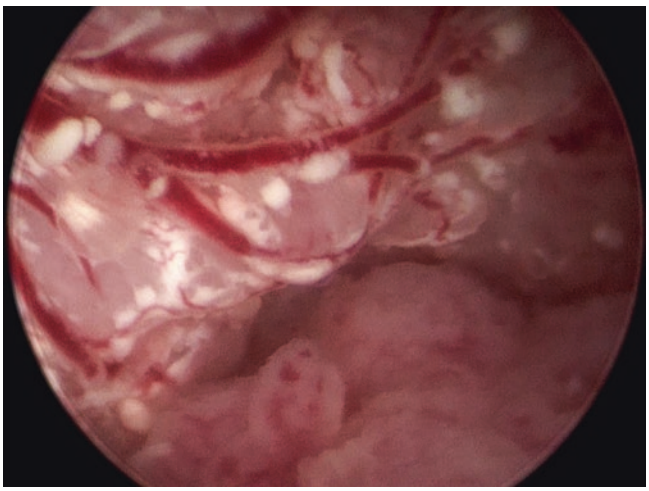

Fig. 15.42 Abnormal vascularization in "vasa nuda pattern." Characteristic image suspected for endometrial cancer (image supplied by A. Di Spiezio Sardo, Md, PhD, University of Federico II, Naples, Italy)

- Better sensitivity and specificity than D&C or transvaginal ultrasound in detection of EC [26–28].
- Direct visualization of the whole uterine cavity, localizing all the focal endometrial lesions and evaluating the extension of the tumor.
- Lower cost of office hysteroscopy compared to operative one.

Moreover the risk of complications in office hysteroscopy is very low: 0.2–1.0% for vasovagal symptoms, 0.01% for infection, and 0.1% for uterine perforation [29]. Instead the risk of uterine perforation in operative hysteroscopy is higher, at 0.1–1.6%, and thus it may be considered as the

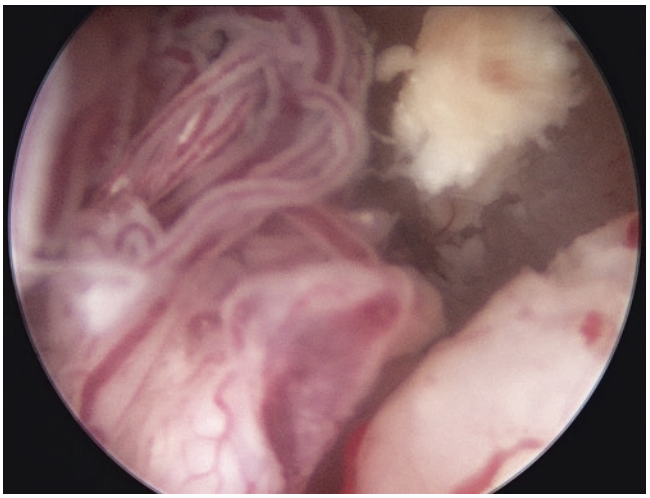

Fig. 15.43 Characteristic vascular "vasa nuda pattern" in endometrial cancer (image supplied by A. Di Spiezio Sardo, Md, PhD, University of Federico II, Naples, Italy)

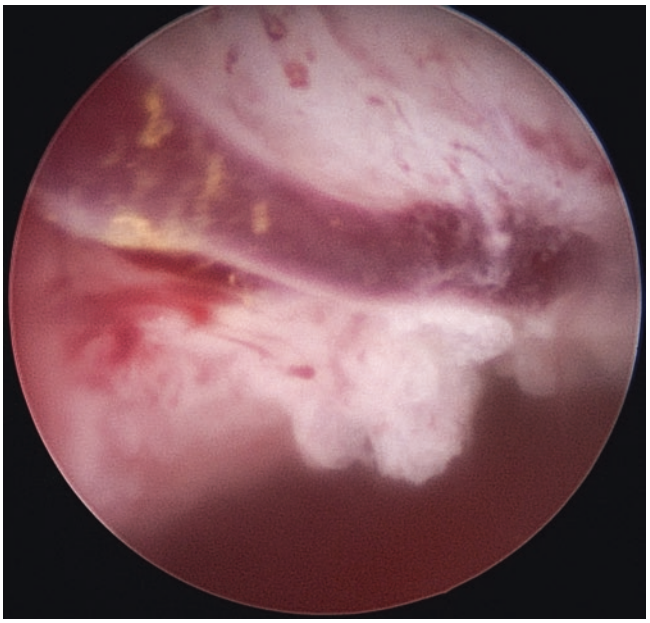

Fig. 15.44 Bridge vessels usually associated with high-risk lesions (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

next step in workup if the office hysteroscopic biopsy is negative in a suspected case of EC.

15.4.4 Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron-Emission Tomography (PET)

The early diagnosis of EC is based on the histological evaluation of hysteroscopic endometrial samples [30]. This cancer is

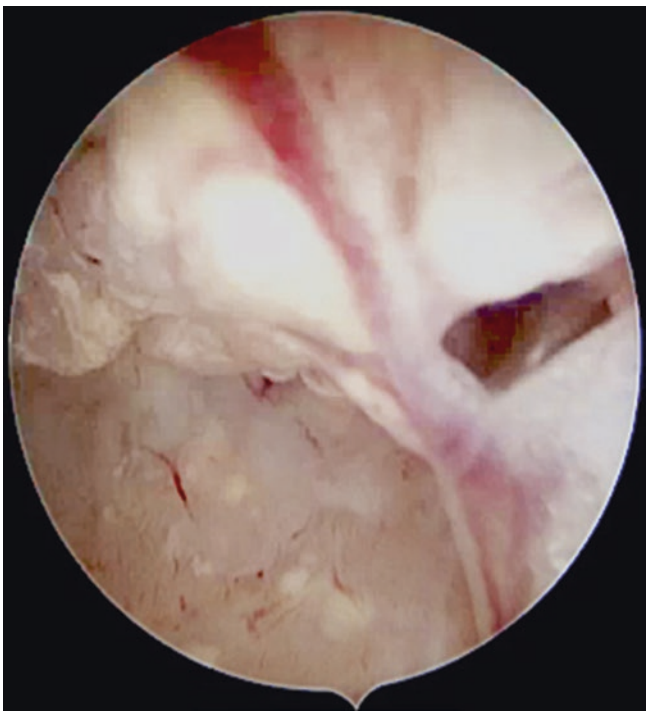

Fig. 15.45 Bridge vessel in mildly differentiated G2 endometrioid adenocarcinoma

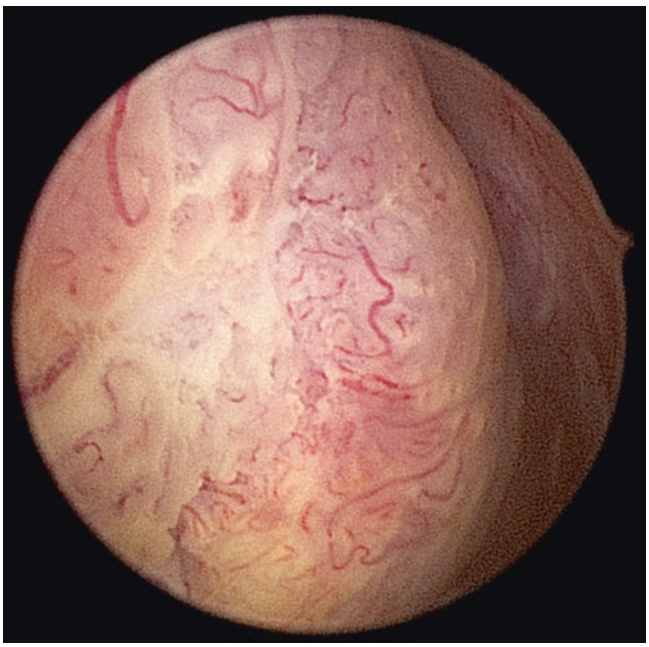

Fig. 15.46 Nodular pattern with characteristic corkscrew vascularization

a surgically staged disease, with most patients having disease confined to the uterus at diagnosis. Therefore, it is not necessary to perform routinely a preoperative instrumental assessment of patients with EC to evaluate eventual metastasis [11]. However, preoperative assessment of metastatic disease with

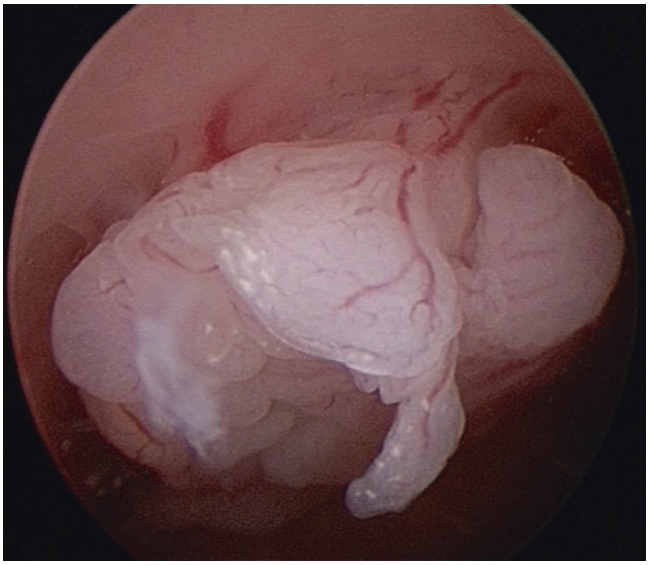

Fig. 15.47 Endometrial cancer arising in endometrial polyp (image supplied by Alicia Ubeda Hernandez, MD, Barcelona, Spain)

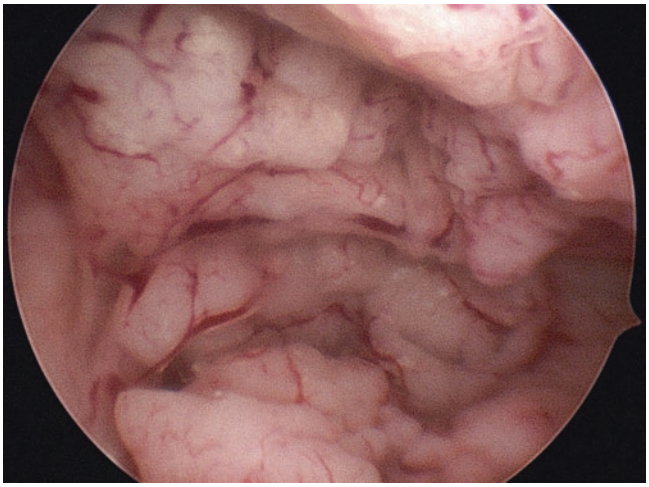

Fig. 15.49 Uterine cavity largely involved by endometrial cancer, suspected for high histologic grade (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

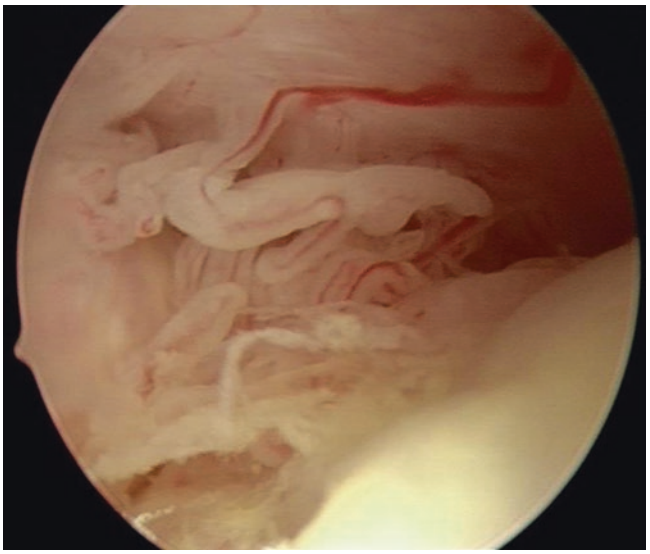

Fig. 15.48 Endometrial cancer arising in the basis of a submucous myoma (image supplied by Alicia Ubeda Hernandez, MD, Barcelona, Spain)

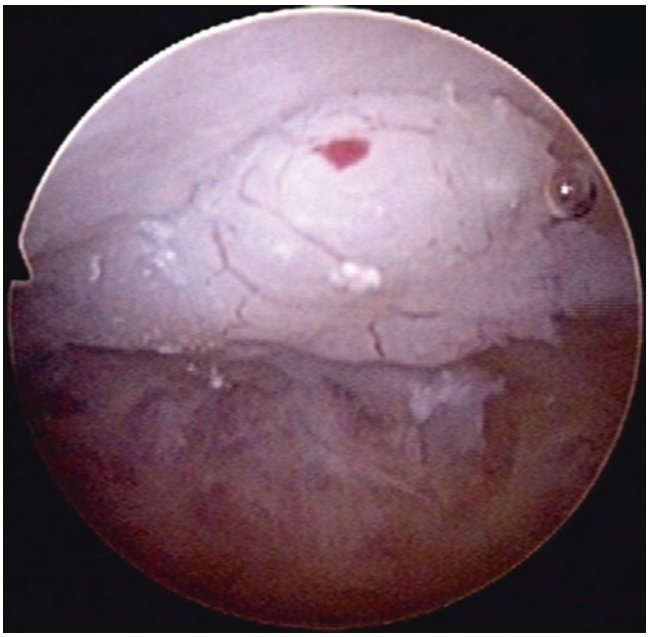

Fig. 15.50 White color shift in grade 1 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

imaging, measurement of serum CA 125, or both may be clinically important in some specific circumstances, such as when the patient has a high surgical risk because of medical comorbidities, when symptoms suggest the possible presence of metastasis in unusual sites, such as bones or central nervous system, and when preoperative histologic diagnosis is of a high-grade carcinoma (including grade 3 endometrioid, papillary serous, clear cell, and carcinosarcoma).

Thus in these cases performing imaging tests may be useful for a correct preoperative evaluation.

MRI with paramagnetic contrast agent is useful to stage endometrial carcinoma, allowing to evaluate the depth of myometrial infiltration with a sensitivity of 87%, the infiltration of the cervical stroma with a sensitivity of 80%, and the involvement of the vaginal walls. It also permits to assess the infiltration of adipose tissue of the parameters and the presence of pelvic or lumbo-aortic lymphadenomegalies in a single method with an accuracy of 76% [31].

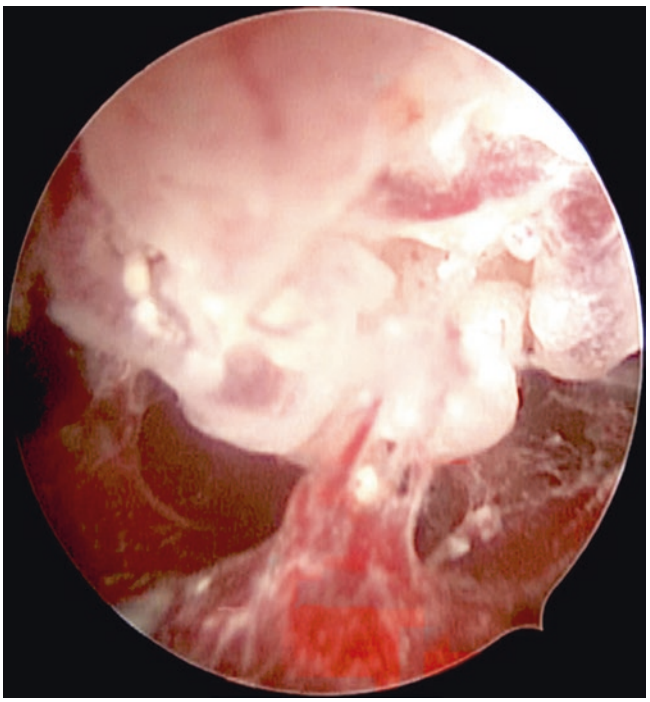

Fig. 15.51 Whitish crumbly voluminous formation, easily bleeding, with increased superficial vasculature. Focal well-differentiated G1 endometrioid adenocarcinoma

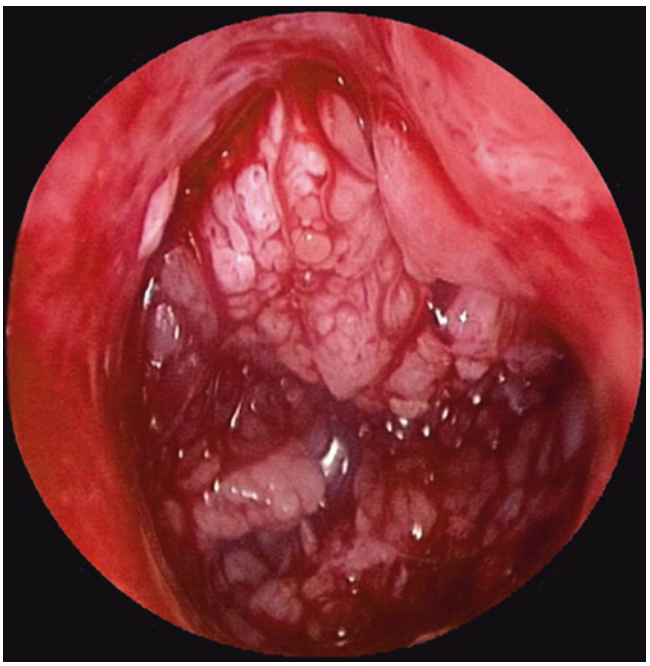

Fig. 15.52 Polypoid endometrial cancer with bleeding areas. View from the isthmus

CT has poor diagnostic accuracy, but it is useful in staging the endometrial malignant pathology, in particular for the study of lymph nodes and liver.

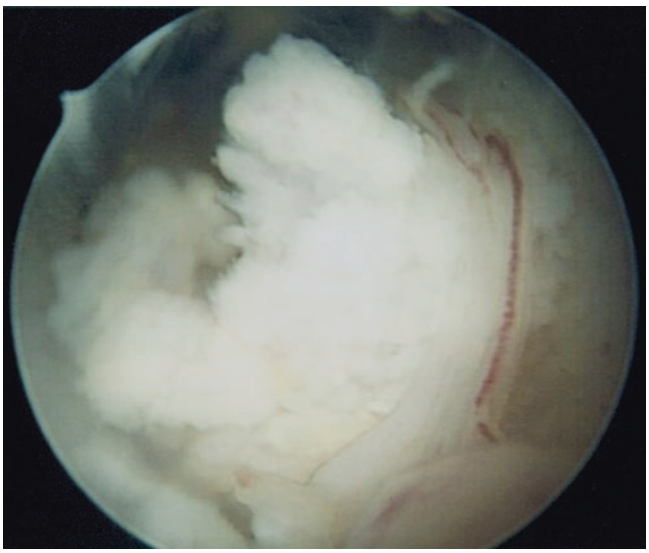

Fig. 15.53 Crumbly whitish exophytic lesion and necrotic areas in mildly differentiated G2 endometrioid adenocarcinoma

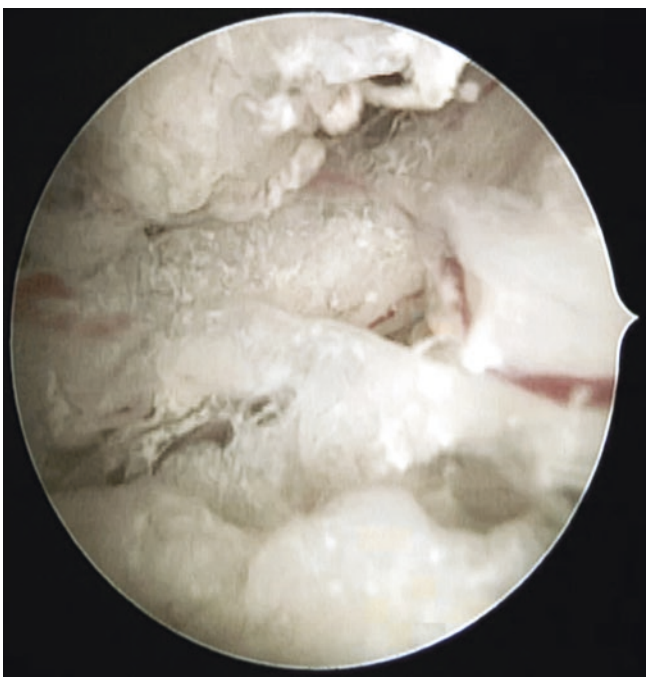

Fig. 15.54 White color shift in well-differentiated G1 endometrioid adenocarcinoma with crumbly surface

In addition to morphological imaging modalities, PET with F-18 fluorodeoxyglucose (FDG) has recently been proposed for the evaluation of EC. This method is used for the detection of lymph nodal metastases (N) [32, 33], during the preoperative evaluation and also during the postoperative follow-up [34]. However it should not be considered in normal clinical practice.

Instead the bone scintigraphy is limited to cases of suspicious bone involvement.

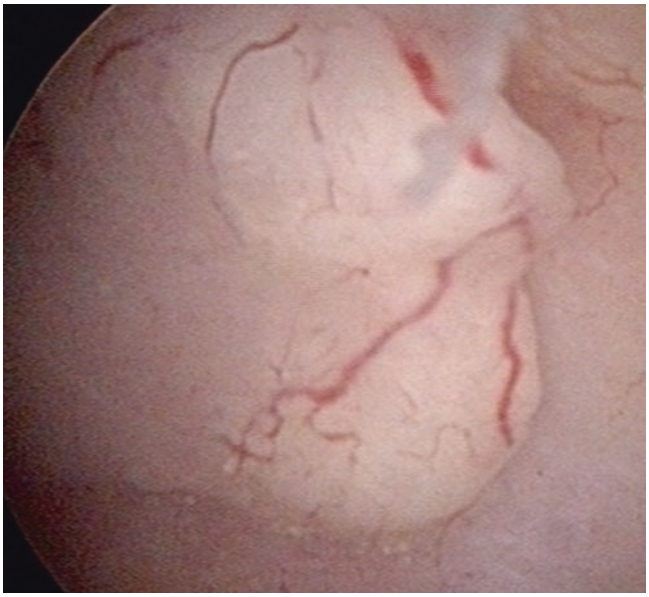

Fig. 15.55 Absent glandular ostia because of high gland-to-stromal ratio in grade 1 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

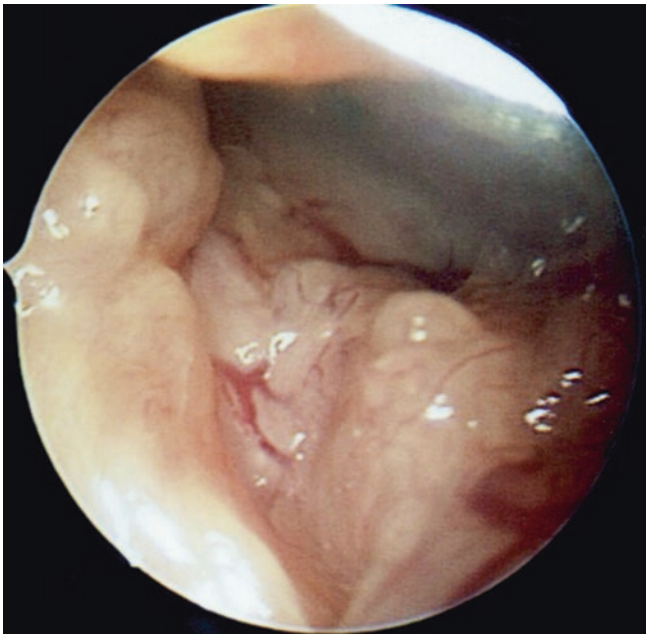

Fig. 15.57 Endometrial cerebroid lesion with vascular ectasia as for angiogenesis phenomenon

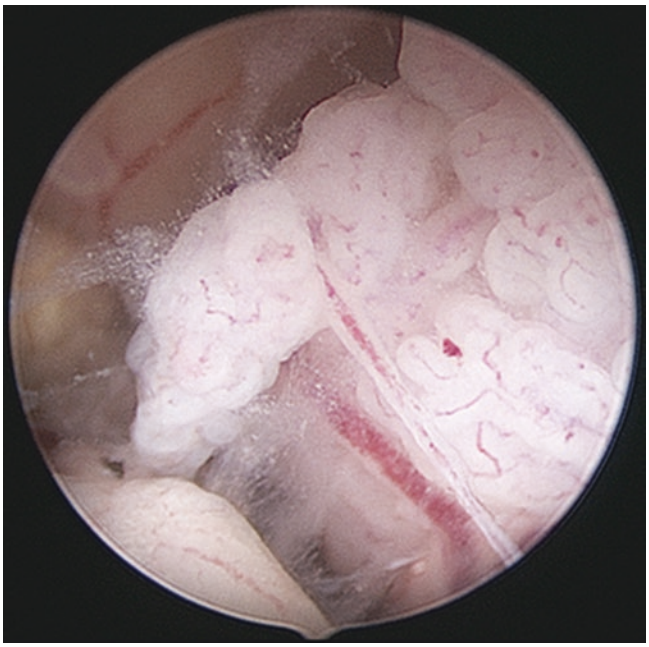

Fig. 15.56 "Cerebroid" mucosal appearance with atypical vascularization

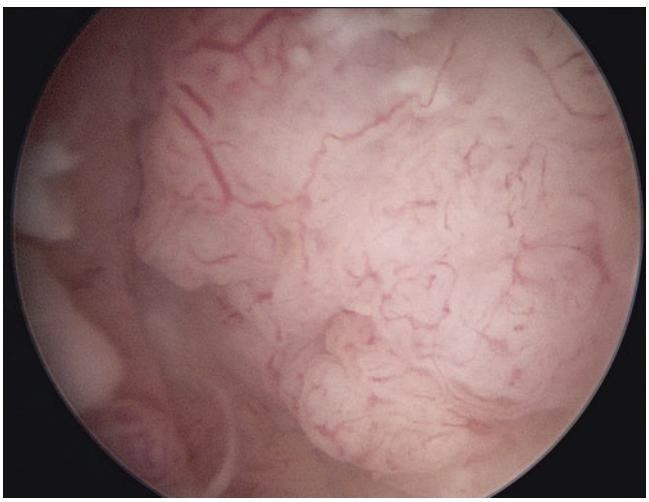

Fig. 15.58 The "cerebroid pattern" is usually associated with endometrial cancer (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

15.5 Staging

As already stated, EC is surgically staged including total hysterectomy, bilateral oophorectomy, and pelvic and para-aortic lymphadenectomy as well as pelvic washing. Pelvic lymphadenectomy typically is defined as removal of the lymph nodes from the distal half of the common iliac arteries, the anterior and medial stretch of the external iliac artery and vein until the point at which the deep circumflex iliac vein crosses the external iliac artery, and the obturator fat pad anterior to the obturator nerve. Instead para-aortic lymphadenectomy is defined as removal of nodal tissue over the distal inferior vena cava from the level of the inferior mesenteric artery to the midright common iliac artery and removal of the nodal tissue between the aorta and left ureter from the inferior mesenteric artery to the midleft common iliac artery [11].

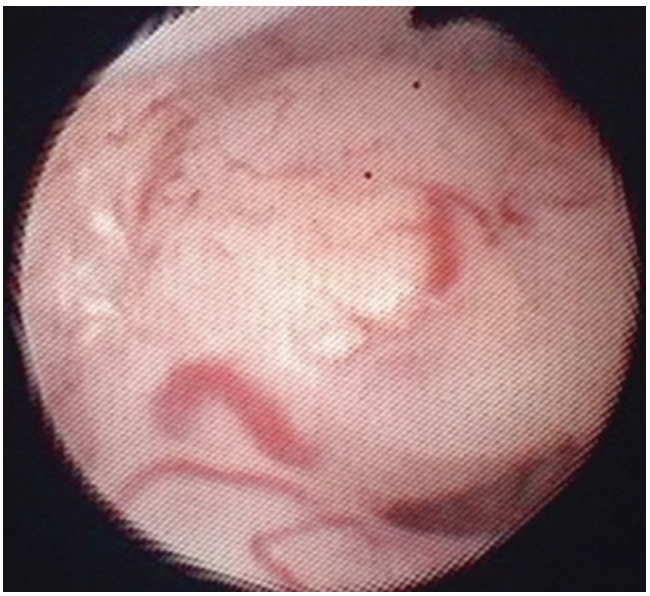

Fig. 15.59 Vascular growth with a "cerebrum-like" feature with bridged formation in grade 1 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

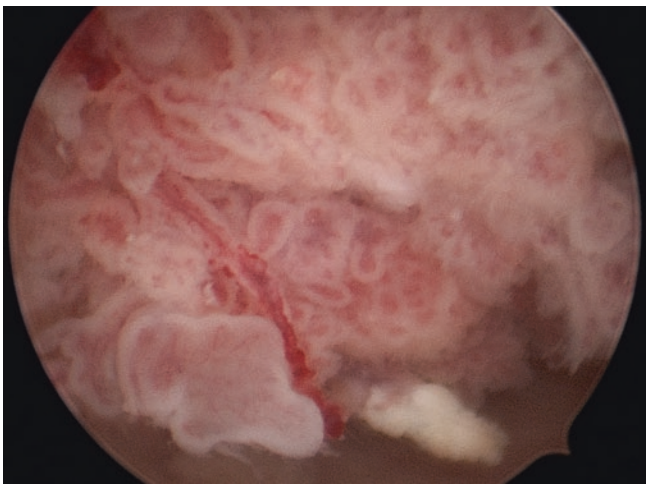

Fig. 15.60 Pseudohyperplastic growth pattern with multiple papillae and "glomerular pattern" (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

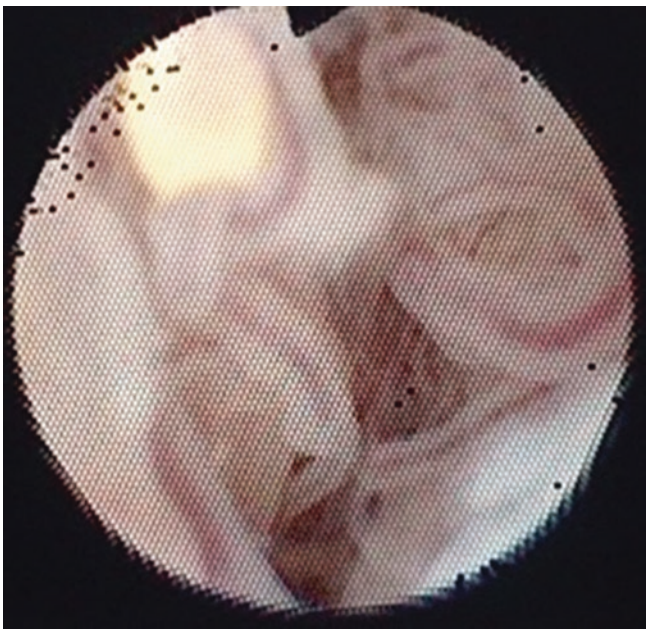

Fig. 15.61 A "glomerular pattern": a polypoid mass presenting with specialized vascular pattern resembling that of a renal glomerulus in grade 3 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

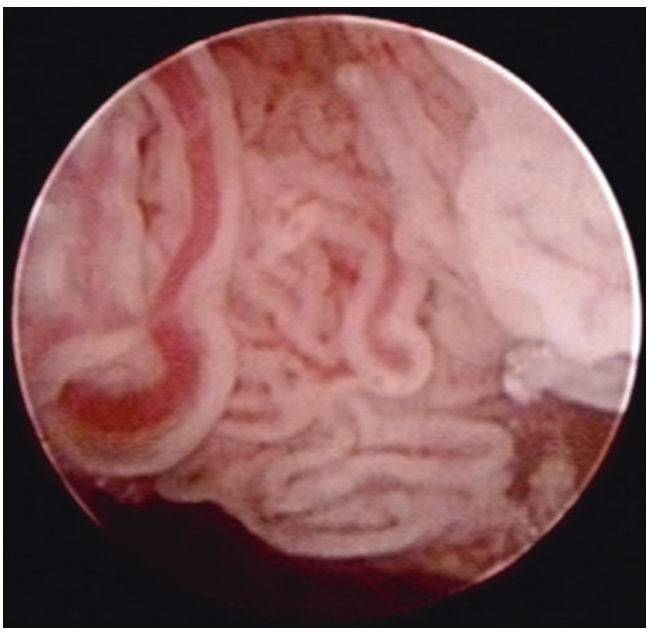

Fig. 15.62 A "glomerular pattern": a polypoid mass presenting with specialized vascular pattern resembling that of a renal glomerulus in grade 3 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

For an adequate dissection of the lymph nodes it is necessary that lymphatic tissue be picked from each side, but a minimum number of nodes has not been established.

The criteria for surgical staging are well defined, but the importance of the extent of the lymphadenectomy is still debated [35].

First of all, it is already discussed whether para-aortic lymphadenectomy should be performed in all patients. Para-aortic nodes may be positive in the absence of pelvic lymphadenopathy [36, 37]. In case of metastatic EC with lymph nodal involvement, the para-aortic lymph nodes are pathological in the 57–67% [36, 38], while involvement of para-aortic lymph nodes, without the pelvic ones, is pres-

Fig. 15.63 A "glomerular pattern": a polypoid mass presenting with specialized vascular pattern resembling that of a renal glomerulus in grade 3 endometrioid adenocarcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

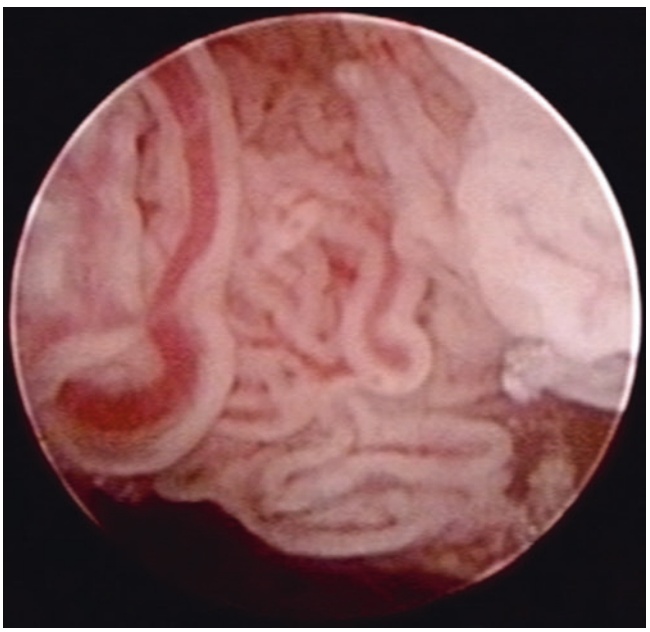

Fig. 15.64 Glomerular pattern (grade 3 tumor) under white light (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

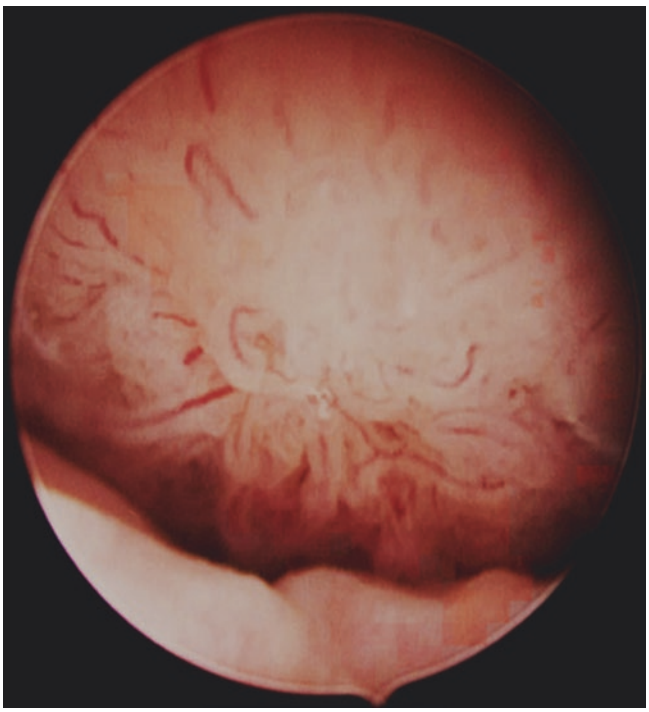

Fig. 15.65 Mildly differentiated G2 endometrioid adenocarcinoma with cerebroid growth pattern and atypical vascular pattern known as "glomerular"

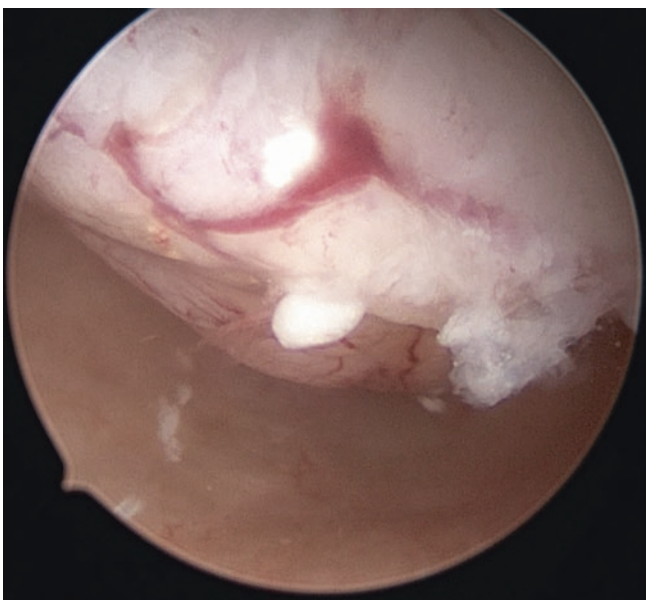

Fig. 15.66 Focal endometrial cancer surrounded by atrophic endometrium (image supplied by A. Di Spiezio Sardo, Md, PhD, University of Federico II, Naples, Italy)

ent in only 16–17% of lymph nodal metastasis [36, 38]. Patients with low-grade disease (e.g., grade 1 and 2 endometrioid lesions with myometrial invasion <50% and tumor size <2 cm) usually do not have lymphadenopathy and do not benefit from a systematic lymphadenectomy [36].

The prior target of EC surgical staging is to define the correct extension of the disease and the consequent patients' prognosis. In more advanced-stage disease the prognosis is worse, requiring additional therapy, and this may not be recognized without comprehensive surgical staging [35].

However a correct surgical staging is not without complications, including the risk of injury to major vessels or

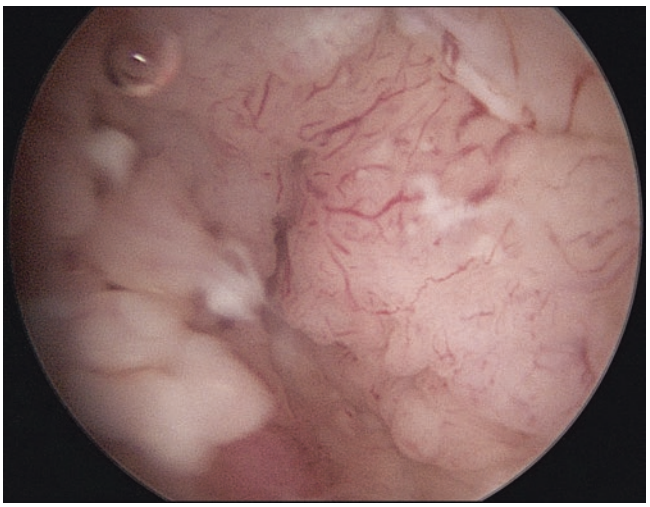

Fig. 15.67 Irregular endometrial surface and increased superficial vascularization surrounded by hyperplastic endometrium (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

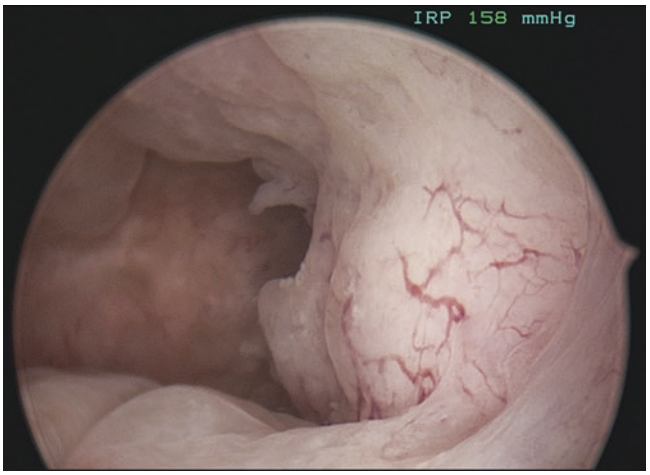

Fig. 15.68 Endometrial cancer surrounded by hyperplastic endometrium. Arborescent vascularization typical of high-risk lesion (image supplied by A. Di Spiezio Sardo, MD, PhD, University of Federico II, Naples, Italy)

Fig. 15.69 Yellowish shift in clear-cell carcinoma (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

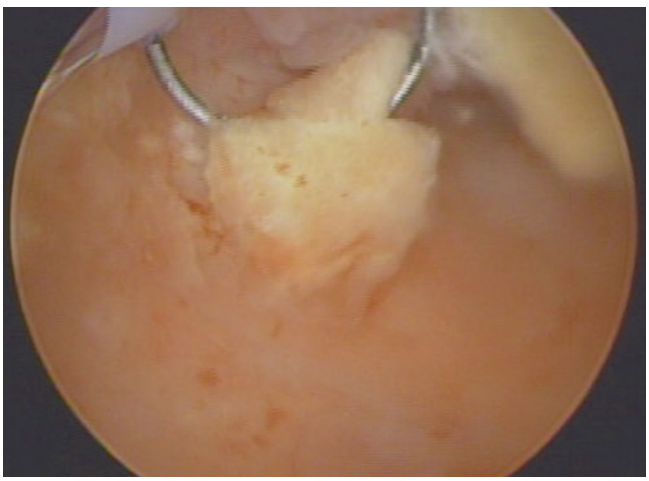

Fig. 15.70 Clear-cell carcinoma presented in yellowish polypoid mass (A. Tinelli et al. (eds.), Hysteroscopy, Springer International Publishing AG, 2018)

nerves, lymphedema, and associated cellulitis. Lymphedema can occur in 5–38% of patients, but it can be avoided by limiting the pelvic lymphadenectomy to superior to the circumflex iliac vein [39, 40].

Clinically stage I may include patients with risk of recurrence; for this reason surgical staging has the advantage to guarantee adjuvant radiation therapy in patients with early-stage disease and recurrence risk, who represent 15–20%. Moreover, 5–9% of patients can be upstaged by surgical staging in terms of extrauterine involvement, modifying prognosis and therapy [36].

There is a benefit in terms of survival rating for patients who undergo para-aortic lymphadenectomy compared with those who don't in women with high-risk cancer. The same effect doesn't exist in patients with low-risk cancer [41]. Anyway there are no randomized trials that encourage lymphadenectomy in early-stage cancer.

Surgical staging of early-stage endometrial cancer is still controversial. The choice between no lymphadenectomy, pelvic lymphadenectomy, and complete pelvic and para-aortic lymphadenectomy is still argued, without clear consensus.

Histology of endometrial biopsies can initially direct patients to surgical treatment with or without lymphadenectomy because it can differentiate the low-grade endometrioid cancer from other histologies, defining the need for a complete surgical staging. Grade 3 endometrioid, papillary serous, clear cell, undifferentiated, and squamous histologies have a worse prognosis and lymphadenectomy is needed

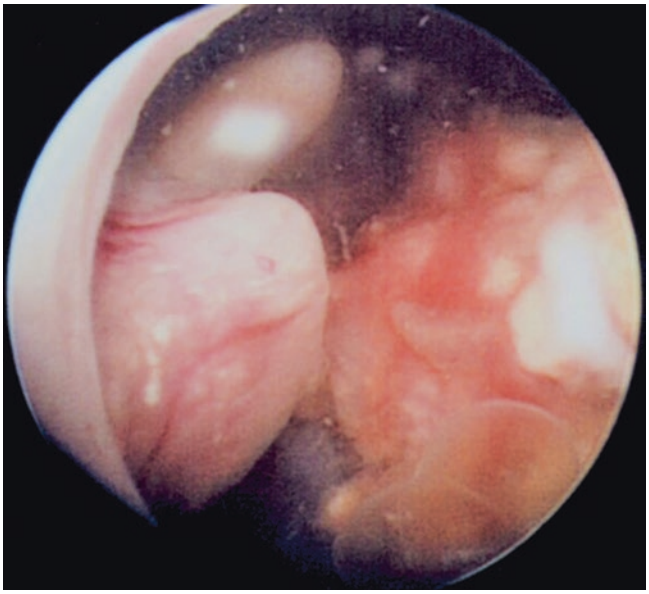

Fig. 15.71 Lobed polypoid formation with smooth surface and no vascular atypia, covering the right uterine wall. Voluminous crumbly bleeding cerebroid lesion involving the left uterine wall with histologic diagnosis of endometrial endometrioid mildly differentiated G2 adenocarcinoma

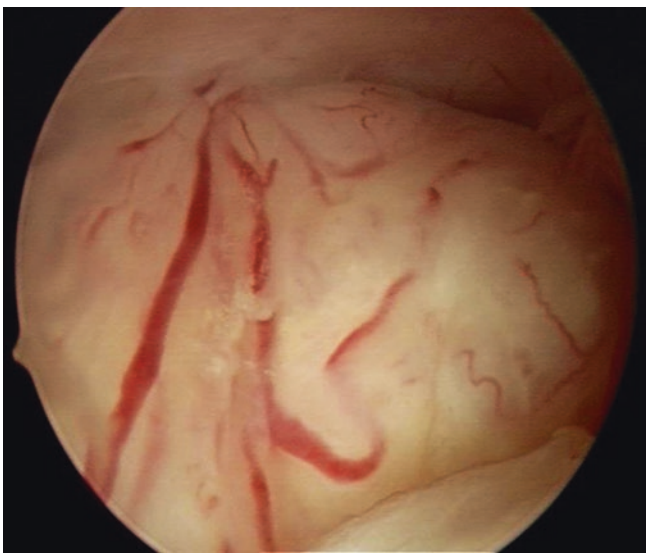

Fig. 15.72 Myoma-like endometrial cancer arising form atrophic endometrium (image supplied by Alicia Ubeda Hernandez, MD, Barcelona, Spain)

[42]. In these histological types of EC advantages of surgical staging overtake the disadvantages.

Further evaluation can be executed intraoperatively because frozen sections can be useful to determine if lymphadenectomy has to be performed in patients with early-stage endometrial cancer, determining the depth of myometrial invasion, primary tumor diameter, grade, and endometrial histology. Patients with low-risk disease (grade 1 or 2, endometrioid histology, myometrial invasion <50%, and primary tumor diameter <2 cm) on frozen section do not require to undergo lymphadenectomy [36, 43].

Table 15.1 International federation of gynecology and obstetrics' surgical staging system for endometrial cancer (2009)

Endometrial cancer (FIGO stadiation of 2009)		
Stage I[a]	**Tumor confined to the corpus uteri**	
Stage IA[a]	No or less than half myometrial invasion	
Stage IB[a]	Invasion equal to or more than half of the myometrium	
Stage II[a]	**Tumor invades cervical stroma, but does not extend beyond the uterus**[b]	
Stage III[a]	**Local and/or regional diffusion of the tumor**	
Stage IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexae[c]	
Stage IIIB[a]	Vaginal and or parametrial involvement[c]	
Stage IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]	
	IIIC1[a]	Positive Pelvic nodes
	IIIC2[a]	Positive Para-aortic nodes involvement with or without pelvic nodes
Stage IV[a]	**Tumor invades bladder and/or bowel mucosa, and/or distant metastases**	
Stage IVA[a]	Tumor invasion of bladder and/or bowel mucosa	
Stage IVB[a]	Distant metastases (including intra-abdominal metastases and/or inguinal lymph nodes)	

[a]Either G1, G2, or G3
[b]Endocervical glandular involvement only should be considered as stage I and no more as stage II
[c]Positive cytology has to be reported separately without changing the stage

15.5.1 Endometrial Cancer Classification

Nowadays the last endometrial cancer staging FIGO, published in 2009, is the most widely used staging system (Table 15.1). It is better than the previous classification published in 1988 because it shows a more accurate and precise distinction among the stages and the substages [44]. This classification does not consider the cellular grading of neoplasia, the involvement of lymphovascular spaces, the positive peritoneal cytology, and the histological type, which are defined as independent prognostic factors. The other staging of endometrial cancer is AJCC classification that is little used [45].

15.6 Treatment

Surgical staging of EC was traditionally performed by laparotomy. Several studies have compared laparotomy with laparoscopy showing that laparoscopy is associated with fewer complications, reduced time of hospitalization, and higher quality of life during the recovery period, but also with longer operative time [46–48].

There are no differences between the surgical approaches in terms of survival rates [49, 50]. Robotic-assisted laparoscopy seems to have similar benefits to classic laparoscopy with a shorter learning curve [51]. Complication rates, laparotomic conversion rates, and length of the recovery period appear similar, while estimated blood loss seems to be lower with the robotic approach [52–54].

Therefore minimally invasive surgery should be considered as the gold standard for the surgical staging of EC.

In case of early-stage cancer (stages I–II), selecting an appropriate adjuvant therapy is not easy and its value in correctly staged patients with risk factors of recurrence is still unclear. Adjuvant radiation for stages I–II reduces the risk of local recurrences, but it does not improve the overall survival [55, 56]. Instead in a high-intermediate-risk group radiation therapy increases progression-free survival, decreasing the frequency of local recurrences.

Factors associated with an increased rate of recurrence are grade 2 or grade 3 disease, lymphovascular space invasion, and outer-third myometrial invasion [57] (Figs. 15.73, 15.74, 15.75, and 15.76). Thus the high-intermediate-risk group included women 70 years or older with one of these risk factors, women 50 years or older with two of these risk factors, and women of any age with all these risk factors.

Among patients who have not received radiation therapy, salvage therapy in case of recurrence is most often curative [58]. Vaginal brachytherapy seems to be equivalent to whole pelvic irradiation in locoregional control and overall survival in patients with high-intermediate-risk factors for recurrent endometrial cancer.

Moreover vaginal brachytherapy has the advantage of having fewer gastrointestinal toxic effects and a better quality of life than whole pelvic irradiation [59]. Therefore this adjuvant therapy should be the treatment of choice in patients

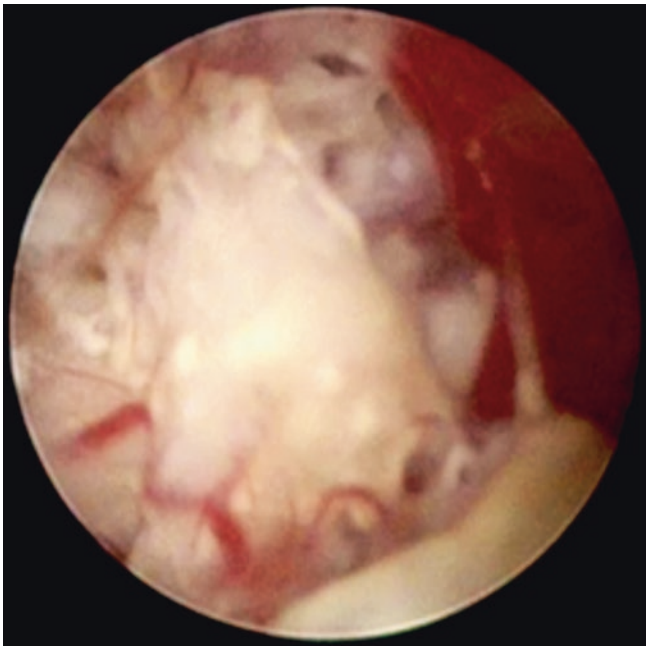

Fig. 15.74 Abnormal growth and vascular ectasia in mildly differentiated G2 uterine cancer

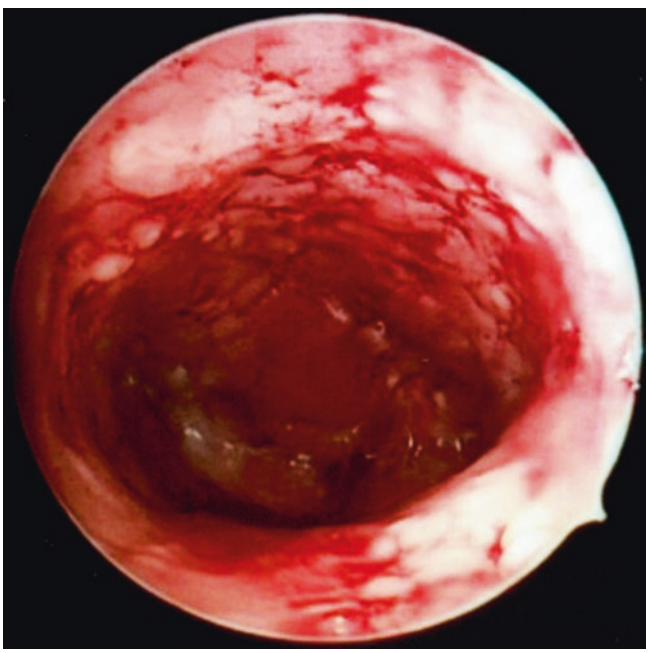

Fig. 15.73 Uterine cavity covered by endometrium with irregular surface and increased vascularization. Histologic diagnosis of mildly differentiated G2 endometrioid endometrial cancer

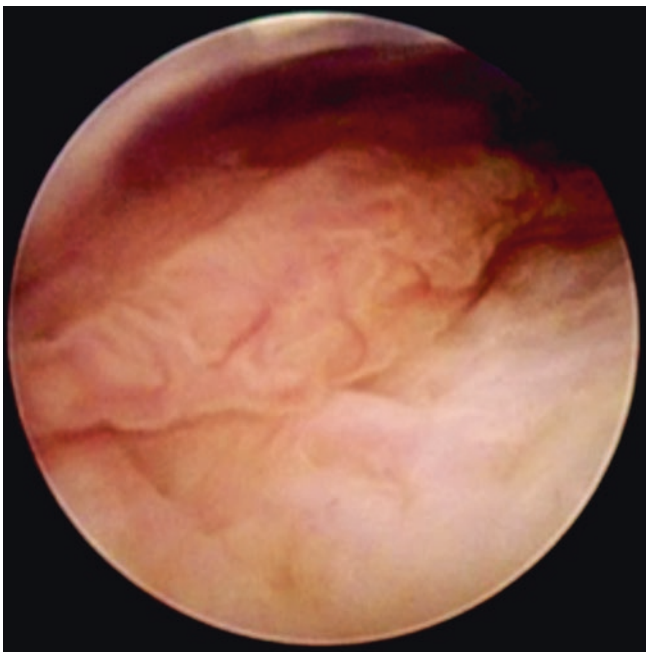

Fig. 15.75 Mildly differentiated G2 uterine cancer protruding through internal uterine orifice

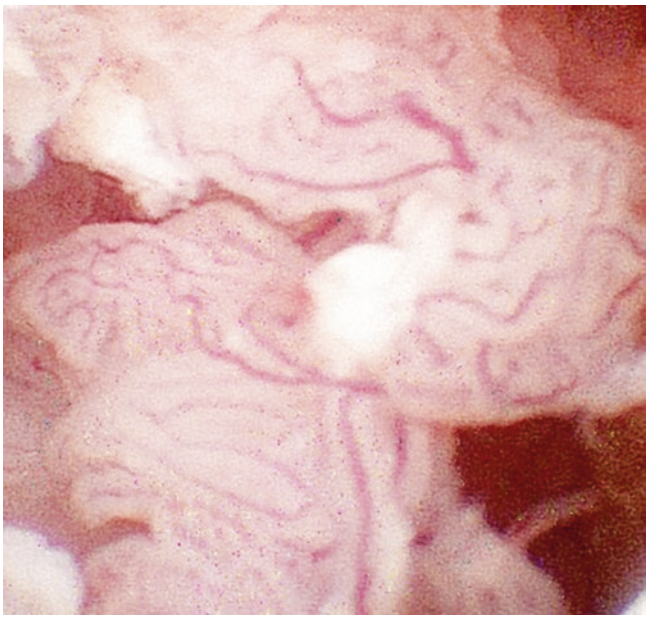

Fig. 15.76 Poorly differentiated G3 endometrial endometrioid cancer with "glomerular pattern"

with early-stage endometrial cancer and high-moderate-risk factors for recurrences.

About 10–15% of new diagnoses of EC involve disease that has spread outside the uterus, accounting for more than 50% of endometrial cancer-related deaths [60]. In these cases the therapeutic approach is multidisciplinary, including surgery, chemotherapy, and radiation therapy, with cytoreduction that seems to be the most important aspect. Indeed, correct cytoreduction (less than or equal to 1 or 2 cm) is associated with an improvement of the overall survival and progression-free rates in patients with advanced-stage or recurrent endometrial cancer [61]. Cytoreduction can be considered as an independent prognostic factor for overall survival in this kind of patients. The extent of residual cancer seems to modify the overall survival of patients with advanced-stage endometrial cancer [62, 63].

Cytoreductive surgery improves progression-free and overall survival also when it is performed for recurrent EC localized to the pelvis or disseminated throughout the abdomen. In this case the type of recurrence (solitary versus carcinomatosis), the ability to perform optimal cytoreduction, and the time lapse from original treatment could determine patients' survival [64]. After secondary surgical cytoreduction median overall survival oscillates from 39 to 57 months [64, 65]. In patients with pelvic recurrence previously treated with radiation therapy, pelvic exenteration is the only curative option, even if it is related to significant postoperative morbidity (60–80%) and mortality (10–15%) [66].

As seen, in advanced- stage endometrial cancer optimal cytoreductive surgery has a therapeutic effect in terms of progression-free and overall survival rates, but patients with metastatic disease have a high risk of recurrence and adjuvant treatment is needed [67]. Combination of chemotherapy and radiation therapy offers better outcomes compared with one of them alone.

Pelvic irradiation with or without extended-field radiation significantly reduces pelvic recurrence, but failures outside the site of radiation are a limit for long-term survival in these cases. Several studies have evaluated the efficacy of combining chemotherapy with radiation therapy.

A randomized trial of radiation therapy followed by chemotherapy in patients with stages III–IV has showed 62–64% recurrence-free survival at 3 years, but completing therapy has not been always possible because of hematologic toxic effects [68].

An acceptable level of toxicity with improved survival has been showed with a "sandwich" combination of radiation and two cycles of chemotherapy (combination of carboplatin and docetaxel or paclitaxel), reporting 79% 5-year survival [69, 70]. Another study has demonstrated 75% 5-year survival in patients with metastases to para-aortic lymph nodes treated with a combination of postoperative chemotherapy and extended-field radiation therapy [71].

Regarding chemotherapeutic drugs used in advanced stages or recurrences of EC, therapeutic schemes with paclitaxel and carboplatin are associated with the same effectiveness of other regimes, but with less toxicity [72, 73].

Chemotherapy is not superior to radiation in locally advanced endometrial cancer; indeed, in these cases brachytherapy represents the standard of therapy after surgery, and it is associated with low rate of local relapse and better disease-free survival. Brachytherapy should not be replaced with chemotherapy alone [74].

Finally first data suggest an interesting role for hormone therapy in patients with advanced-stage or recurrent endometrial cancer that cannot be treated with more aggressive therapies [75].

15.7 Conservative Treatment

As already stated, the standard therapy of EC includes total hysterectomy and bilateral salpingo-oophorectomy (with or without pelvic and para-aortic lymphadenectomy, according to cancer grade and stage) [76]. Despite surgical treatment being a highly effective approach, it causes a permanent loss of reproductive potential [77].

Approximately 20% of EC are diagnosed in premenopausal women and 5% in women up to 40 years of age. As several studies have shown, its incidence is rising among young women, reaching 1% for year. Moreover the frequency of pregnancies achieved by women in advanced age is increasing continuously, also thanks to assisted reproductive technologies, and so EC is often diagnosed in patients

who have not fulfilled their reproductive plan, highlighting the importance of fertility preservation in this population.

In younger and premenopausal women endometrial cancer is often diagnosed at early stage with low grade and only uterine involvement, determining a better prognosis than older patients [78, 79].

Nowadays fertility-preserving treatments offered to young women with EIN and early-stage EC without myometrial involvement are limited to hormonal methods, because there are no statistically significant data about the management of these patients [80, 81].

In these cases the main proposed treatment is represented by the use of progestins, while other drugs such as gonadotropin-releasing hormone agonists, antiestrogens, and aromatase inhibitors have been rarely used [82]. The effects of this therapy on endometrium are well known and they are secretory differentiation with inhibition of estrogen receptor function, maybe inhibition of endometrial cell mitosis with increase of apoptosis, and finally some progestins having an antiangiogenic effect.

A better understanding of molecular mechanisms of progestin action in EC responding to hormonal treatment would be helpful to improve response rates to these drugs.

Thus, it will be important to study better the progestin effect on malignant cells and also on neighboring cells, including stromal, endothelial, and immune cells that can influence the tumors. Moreover as risk factors and incidence of EC are rising, progestins could be effectively used also to prevent EC in the high-risk population with variable success [83–86].

An alternative approach to progestinic therapy alone combines operative hysteroscopy and hormonal therapy. Medroxyprogesterone acetate (MPA), megestrol acetate (MA), and, more recently, levonorgestrel intrauterine device (LNG-IUD) are the most commonly used progestins. The dose (for oral drugs) and duration of treatment are, however, not yet standardized. Finally, data on conservative strategy are still limited, mostly based on small retrospective series generally in the absence of long-term treatment outcomes [87].

The choice of progestin and its method of delivery should be dictated by its expected efficacy as well as side effects and patient tolerability. Orally administered progestins are not without side effects, including thrombus formations, mood alterations, headache, weight gain, and breast pain and/or tenderness. Progesterone therapy is contraindicated in those with a thromboembolism history, breast cancer, or hepatic dysfunction [88]. The progesterone-releasing IUD is a means to generate a localized effect within the endometrium while avoiding the adverse systemic toxicity. The levonorgestrel-releasing intrauterine system (Mirena) releases 20 mcg of levonorgestrel per day [89].

According to published evidence of fertility-sparing options [90], the average response time seems to be 12 weeks [91] with a complete response time of 6 months [92]. Recurrence after an initial response has been noted in 24% with a median time of 19 months [93].

Treatment with oral progesterone or the LNG-IUS should be for a minimum of 6 months in order to induce histological regression of malignant lesions. In case of LNG-IUS the women should be encouraged to retain it for up to 5 years or the research of a pregnancy. During the treatment, surveillance should include hysteroscopic endometrial biopsies performed every 3 months until two consecutive negative biopsies are obtained [94].

Despite the large body of literature available for the management of EC, there is no standardized consensus about diagnosis, treatment, and follow-up of patients with early stage of endometrial adenocarcinoma.

The preoperative evaluation of the neoplastic stage is clinically important because each disease should be matched with an appropriate intervention in order to avoid undertreatment or overtreatment. Selecting the “appropriate” population represents actually the most important factor for safety and effectiveness of conservative treatment.

Endometrial hyperplasia (EH) is traditionally considered a continuum of morphologic changes beginning with simple glandular/stromal overgrowth (simple hyperplasia) and ending with complex, highly atypical histologic and cytologic proliferations with a precancerous behavior (complex atypical hyperplasia). According to the literature, the estimated progression of atypical hyperplasia to carcinoma is 30% at 10 years [95].

Actually the preferred terminology to define this last type of lesions is “endometrial intraepithelial neoplasia” rather than “atypical endometrial hyperplasia” [11].

Precancerous endometrial lesions arise focally, as the result of a clonal outgrowth of genetically mutated glands with a cytologic and architectural pattern different from the background endometrium. They can only be recognized through a combination of newly histologic features which define the entity of endometrial intraepithelial neoplasia (EIN). This assumption has changed endometrial precancer diagnosis.

The term EIN is not used as synonymous of carcinoma but it indicates a lesion that may regress, persist, or progress to invasion.

In interested areas of the endometrium, EIN cells are already neoplastic with a monoclonal growth pattern and clonally distributed mutations.

Approximately one-third of women with EIN will have a concurrent carcinoma diagnosed within the first year, and the long-term cancer risk is 45 times increased beyond benign endometrial hyperplasia [96–98].

Pathologic criteria have been modified in order to clearly distinguish the different clinicopathological entities which have to be managed differently.

As recently supported by ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer, assessment of clinical and pathological characteristics of the tumor is important to select the appropriate medical intervention.

According to several studies, hysteroscopy has not only a diagnostic role but also a therapeutic one. Myometrial invasion is rarely evident in a traditional endometrial curettage or biopsy, because these techniques do not succeed in sampling the underlying myometrium.

The presence of myoinvasion is diagnostic of adenocarcinoma and so in the initial stage should be confirmed by enhanced pelvic magnetic resonance imaging (MRI) to exclude overt myometrial invasion, as well as adnexal or pelvic node involvement. Most of all, during operative resectoscopic hysteroscopy, endometrium–myometrium biopsies can be performed in order to histologically exclude myometrial invasion or lymphovascular space invasion (LVSI), resulting in an appropriate selection of patients for the conservative treatment.

However, a set of strict selection criteria have to be respected to correctly choose patients for fertility-sparing treatment [93]: grade 1 well-differentiated tumor, absence of LVSI, no evidence of myometrial invasion, no evidence of metastatic disease, no evidence of suspicious adnexal mass, absence of lymphadenopathy, anamnestic exclusion of hereditary non-polyposis colorectal cancer (HPNCC)/Lynch II syndrome, and no contraindication to medical treatment.

At the beginning the patients have to be correctly informed about risks of persistence, progression, and recurrence and about periodic follow-up, which can be prolonged for many years.

In literature, several authors proposed to combine hormonal treatment to conservative hysteroscopic treatment. In young patients affected by EIN or well-differentiated endometrioid adenocarcinoma, resectoscopic surgical treatment allows to select patients who would benefit from progestinic treatment, evaluating myometrial infiltration and determining a cancer cytoreduction.

15.7.1 Hysteroscopic Conservative Management of Early Endometrioid Adenocarcinoma in Younger Patients

In literature, resectoscopic resection has already been proposed as a preliminary surgery step in order to achieve neoplastic cytoreduction and accurate histologic diagnosis, increasing neoplasia response rate, when combined to progestins, and improving subsequent reproductive outcome.

Mazzon et al. have proposed an innovative conservative treatment by hysteroscopic tumor resection, followed by progestinic therapy, in six patients with focal well-differentiated endometrial adenocarcinoma stage IA. They underwent hysteroscopic resection of the neoplastic lesion, the endometrium near the lesion, and the myometrium under the lesion (3–4 mm). Moreover, random endometrial-myometrial biopsies of uterine walls were performed for histopathological analysis [99]. The hysteroscopic treatment was followed by hormonal therapy with megestrol acetate (160 mg/day) for 6 months.

In our clinical practice, we have proposed hysteroscopic removal of localized endometrial neoplastic lesion before medical treatment in young women desiring childbearing and with a diagnosis of EIN or well-differentiated G1 endometrioid adenocarcinoma stage IA. Eligible patients should have no evidence of neoplastic spread over the mucosa. After a complete counselling, operative hysteroscopy has been performed under general anesthesia, using a 26 FR resectoscope (Karl Storz) with a 0° lens. Distension of the uterine cavity has been obtained using sorbitol-mannitol solution. The resectoscopic technique, described by Di Spiezio et al., consists of [100]:

- Resection of the exophytic lesion including the first 3–4 mm of myometrium underneath the lesion
- Enlargement of the resection to the endometrium adjacent to the lesion
- Multiple random endometrial–myometrial biopsies

According to our purpose of management, if the pathologic analysis confirmed a focal EIN or well-differentiated G1 endometrioid adenocarcinoma without myometrial invasion, hormone therapy with megestrol acetate (160 mg) daily (or alternatively, LNG-IUS) is initiated and prosecutes for 9 months.

Surveillance scheme is based on every-3-month diagnostic hysteroscopy with biopsy, defining a complete remission when hysteroscopic biopsies result negative 3 months after the end of therapy. At this point, patients have to attempt a childbearing spontaneously or by assisted reproductive technology. If the pathology persists, patients undergo hysterectomy.

After complete remission, the patients are closely followed by every-3-month diagnostic hysteroscopy with biopsy during the first year of follow-up, and then every 6 months. The duration of follow-up has not been yet established and, in literature, the mean relapse time has been reported to be 20 months [91].

In case of recurrence, a further hysteroscopic treatment could be proposed for surgical resection followed by hormonal therapy, despite being based on few cases.

As the presence of myometrial infiltration is an exclusion criterion for conservative treatment worsening the prognosis and increasing the risk of lymphonodal involvement, there are no reports of conservatively treated low-grade endometrial cancer with minimal myometrial involvement. Thus, for the

first time we published a case series of three young women seeking pregnancy with diagnosed well-differentiated G1 endometrioid adenocarcinoma with minimal myometrial invasion (1–2 mm) treated with conservative hysteroscopic surgery. After a proper counselling on risks of intervention, progression, and recurrence of disease, the patients underwent conservative management, as previously described, with a 5-year follow-up [101].

The subsequent 5-year follow-up negative for neoplasia and the pregnancies achieved by our patients may indicate this temporary fertility-sparing treatment as a new short-term alternative before the definitive surgical management in highly motivated EC patients with superficial myometrial invasion and not still fulfilled desire of childbearing. More studies are necessary to confirm these preliminary data.

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Part III

Hysteroscopy and Abnormal Uterine Bleeding (AUB)

16

Sergio Haimovich and Roberto Liguori

16.1 Introduction

About 30% of nonpregnant women suffer from an AUB during reproductive age. Classic terminology for AUB was insufficient and confusing [1, 2] (Figs. 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 16.10, and 16.11).

In 2011 the International Federation of Gynecology and Obstetrics (FIGO) published a new classification of AUB (*PALM COEIN* classification) based on both etiology and grade of severity of AUB [3] (Tables 16.1 and 16.2).

The goal of this new classification, designed by an international group coming from 6 continents and over 17 countries, is to facilitate the clinical care and research on AUB by a standardized method of investigation [4–6].

Old terminologies as menorrhagia, metrorrhagia, dysfunctional uterine bleeding, and polymenorrhagia became obsolete.

In 2018 there was a revision of classification of underlying causes of AUB (PALM COEIN) and highlights of changes are summarized [7].

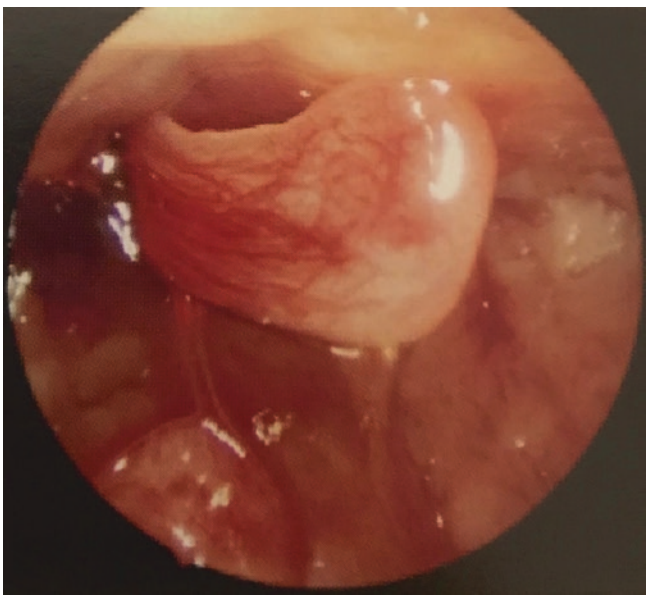

Fig. 16.1 Cervical polyp

Fig. 16.2 Endometrial polyp

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_16

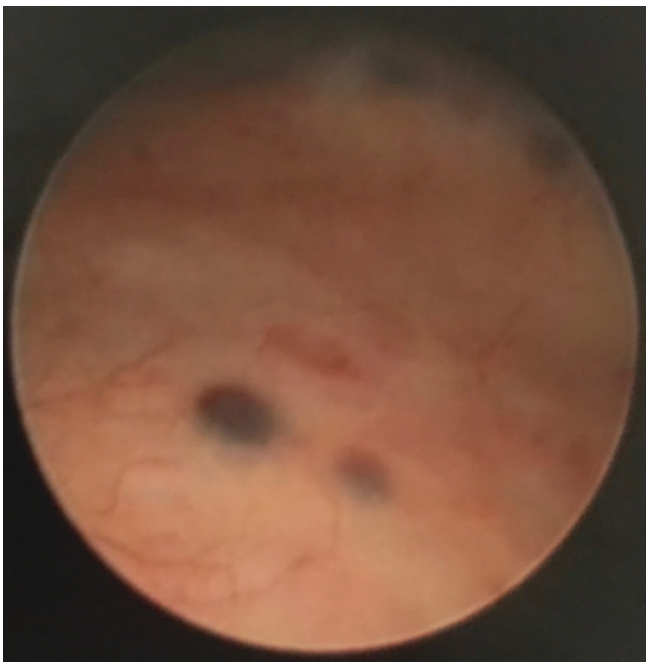


Fig. 16.3 Adenomyosis

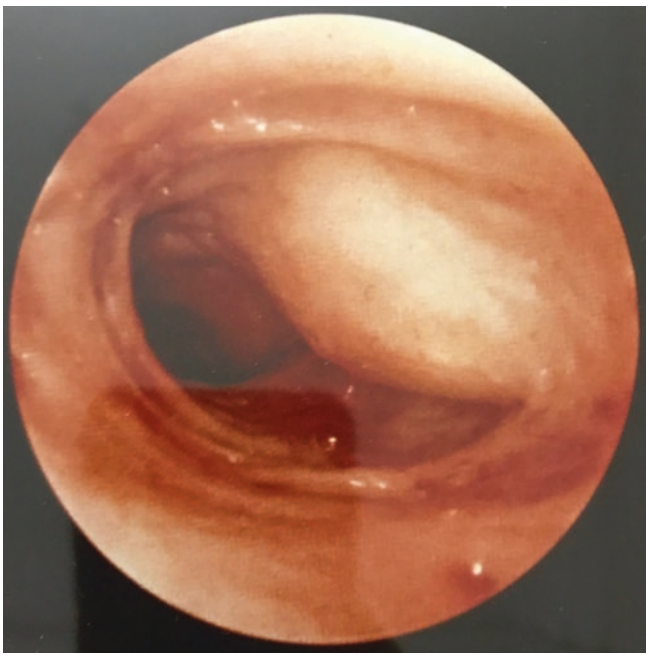


Fig. 16.5 Submucous myoma G1

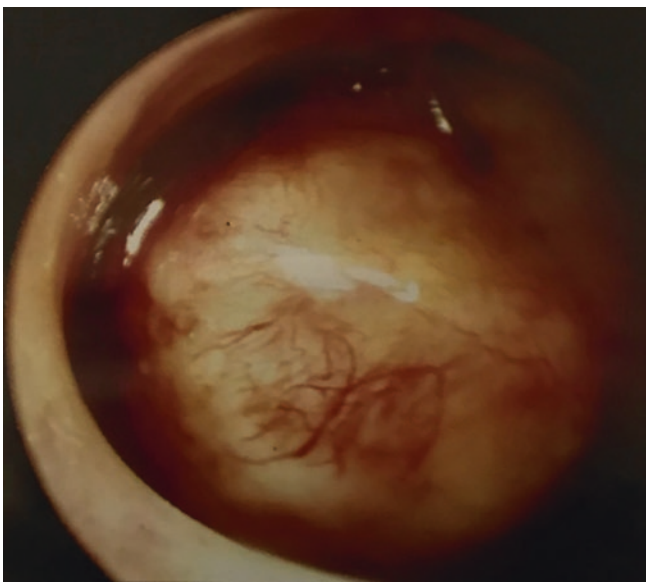


Fig. 16.4 Submucous myoma G0

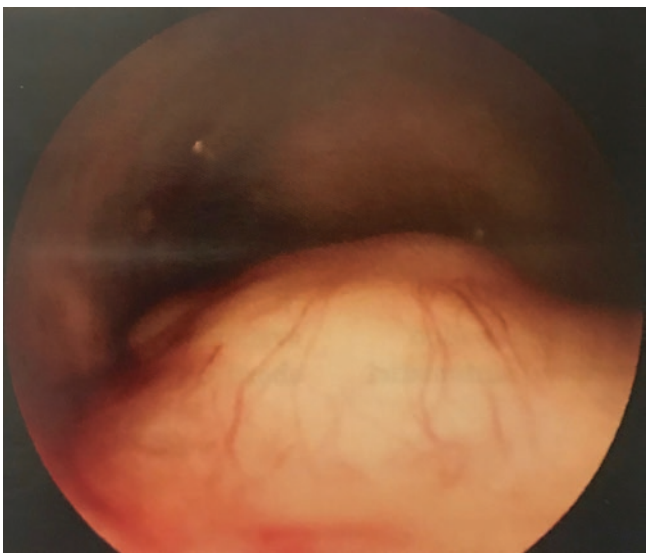


Fig. 16.6 Submucous myoma G2. *Courtesy of Dott. Raffaele Paoletti, MD, Italy*

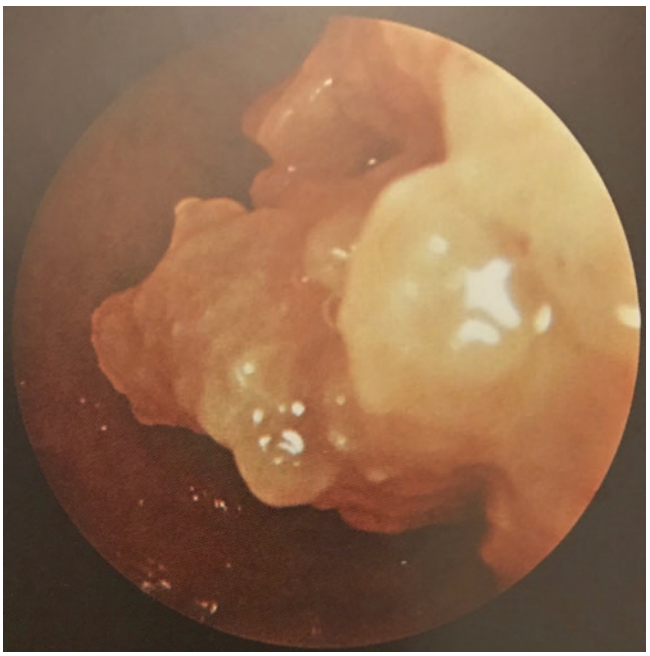


Fig. 16.7 Endometrial hyperplasia

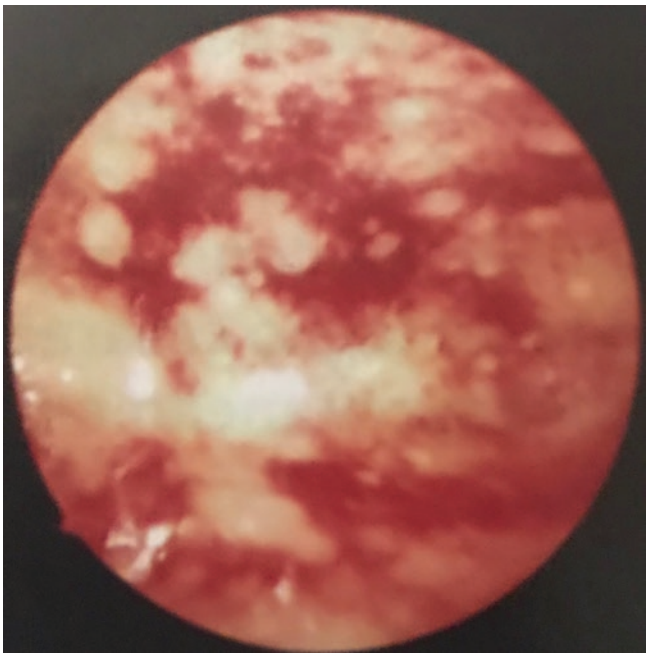


Fig. 16.9 Endometritis

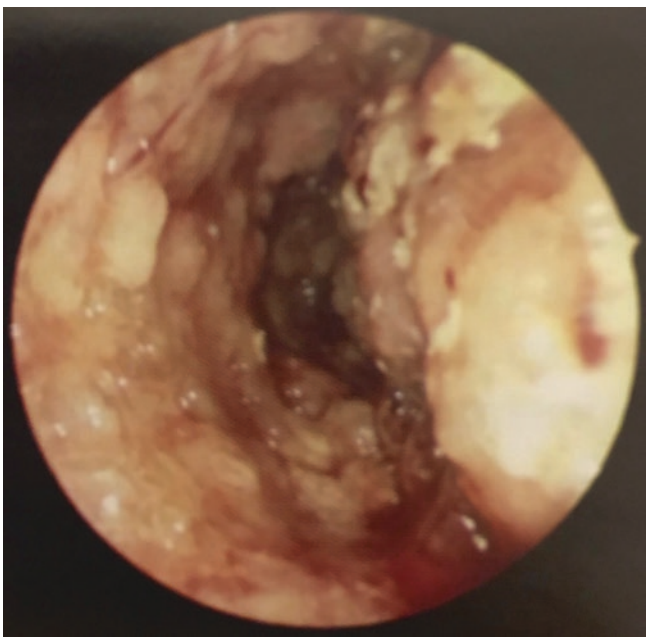


Fig. 16.8 Endometrial cancer

Fig. 16.10 Isthmocele

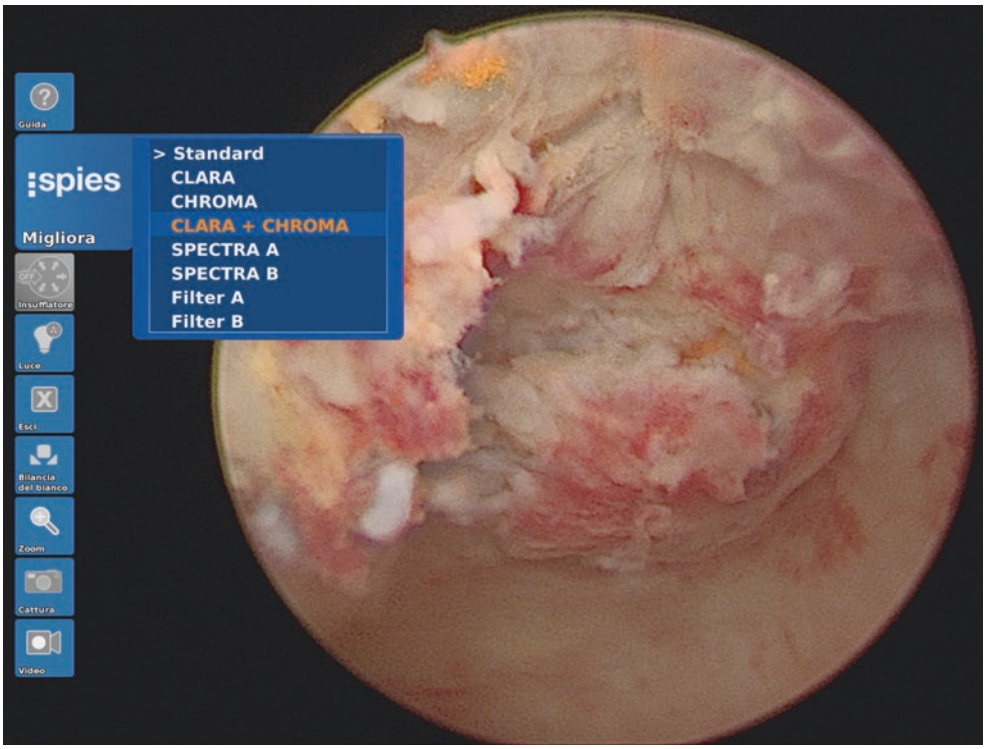
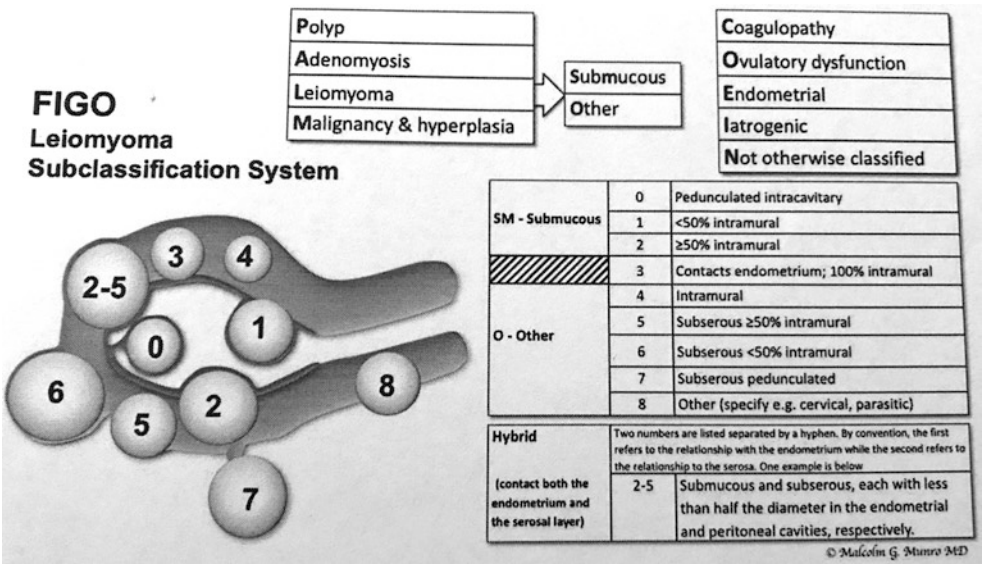


Fig. 16.11 MAV. *Courtesy of Dott. Stefano Calzolari, MD, Italy*

Table 16.1 PALM COEIN classification 2011


FIGO
Leiomyoma
Subclassification System
Polyp
Adenomyosis
Leiomyoma
Malignancy & hyperplasia
Submucous
Other
Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not otherwise classified
SM - Submucous
0 Pedunculated intracavitary
1 <50% intramural
2 ≥50% intramural
3 Contacts endometrium; 100% intramural
O - Other
4 Intramural
5 Subserous ≥50% intramural
6 Subserous <50% intramural
7 Subserous pedunculated
8 Other (specify e.g. cervical, parasitic)
Hybrid
(contact both the endometrium and the serosal layer)
Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below
2-5 Submucous and subserous, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.
© Malcolm G. Munro MD

16.2 Endometrial and Cervical Polyps (AUB-P)

Is it a frequent disorder in reproductive age They are often asymptomatic but sometimes are a common cause of AUB [8].

Diagnosis is based on US, SIS, HYS, and histopathology.

Usually polyps are benign but in a small percentage they may have atypical or malignant features even in young women [9, 10].

The use of small-diameter hysteroscopes and resectoscopes allows these procedures to be performed as a single-stage "see and treat" in the comfort and safety of an office-based setting.

Table 16.2 PALM COEIN classification 2018

System 2 category	Change
AUB-A	Refined sonographic diagnostic criteria
AUB-L	Inclusion of Type 3 as a submucous leiomyoma
	Type definitions and distinctions
	Distinction between Types 0 and 1; 6 and 7
	Distinction between Types 2 and 3; 4 and 5
AUB-C	No longer includes AUB associated with pharmacologic agents that impair blood coagulation which are now included in AUB-I
AUB-I	Now includes AUB associated with all iatrogenic processes including the use of pharmacological agents used for anticoagulation and those thought to interfere with ovulation.
AUB-O	Diagnostic threshold changes based upon the revisions of System 1, described above.
	No longer includes ovulatory disorders associated with drugs known or suspected to interfere with ovulation
AUB-N	The name of the category has been changed from "Not Yet Classified" to Not Otherwise Classified.
	There is a brief discussion of a potential new cause of AUB the so-called uterine "niche" or isthmocele following lower segment cesarean section

Abbreviations: AUB, abnormal uterine bleeding; FIGO, International Federation of Gynecology and Obstetrics.

16.3 Adenomyosis (AUB-A)

Adenomyosis is a common gynecological disorder in women in reproductive age characterized by the presence of ectopic endometrial glands and stroma within the myometrium [11].

Prevalence ranges from 5% to 70% and the relationship between adenomyosis and AUB is unclear in the literature.

In the past the only way to confirm adenomyosis was to examine uterus after hysterectomy.

Today pelvic imaging such as MRI and US with specific diagnostic criteria and adequate skills of operators can detect some orienting signs [12, 13].

It is demonstrated that the two-dimensional transvaginal ultrasonography has similar sensitivity and specificity for diagnosis of adenomyosis when compared to MRI [14–17].

Hysteroscopy is not a first-line diagnosis and treatment approach for adenomyosis and it represents a viable option only in selected cases of focal or diffuse superficial forms [18].

During office hysteroscopy it is possible to enucleate superficial focal adenomyomas or to evacuate hemorrhagic cystic lesions of less than 1.5 cm of diameter.

Resectoscope approach is indicated in cases of superficial adenomyotic nodules >1.5 cm in size and for diffuse superficial adenomyosis.

16.4 Leiomyoma (AUB-L)

Uterine fibroids are the most frequent tumors in women in reproductive age.

These are often asymptomatic but as polyps are responsible for AUB [19–21].

It is mandatory to define:

- Number
- Dimension
- Size (submucosal, intramural, subserosal)
- Uterine localization (upper segment, lower segment, cervix, anterior, posterior, lateral)

AUB is a typical and frequent symptom of submucosal myomas due to the distortion of the wall and the increase of the endometrial surface. The distortion is seen by US.

Diagnosis is confirmed by hysteroscopy. The histology in most of the cases is benign although in some rare cases a malignant degeneration could happen.

In the PALM COEIN 2018 revision, a subclassification of uterine fibroids is also planned.

16.5 Malignancy and Hyperplasia (AUB-M)

Although it is an uncommon pathology among young women, it is responsible for AUB.

Diagnosis is suspected during US but is confirmed by histology, using aspiration biopsy such as Cournier or Pipelle, but also by directed biopsy performed by hysteroscopy [22–24].

In some selected cases specially in infertile patients it is possible to offer hysteroscopic treatment but always followed by a mandatory follow-up.

16.6 Coagulopathy (AUB-C)

This terminology includes various hemostasis disorders often associated with AUB [25–30].

Most common causes are:

- von Willebrand
- Glanzmann thrombasthenia
- Thalassemia major

Among adolescents, around 10% will have a coagulation problem with AUB.

The use of tranexamic acid may be of benefit for some.

16.7 Ovulatory Dysfunction (AUB-O)

Endocrinological disorders such as polycystic ovary syndrome, thyroid disorders, hyperprolactinemia, obesity, weight loss, or at the extremes of reproductive age adolescence, and premenopausal age, are often associated with AUB [31].

Sometimes etiology can be due to iatrogenic causes such as users of phenothiazines and tricyclic antidepressants; these latter drugs are now included in the PALM COEIN classification of 2018, in iatrogenic category.

16.8 Endometrial (AUB-E)

When AUB occurs and no definable causes are suspected, it is probably the presence of a primary disorder of endometrial hemostasis due to deficiencies in local production of some substance vasoconstrictors as endothelin-1 or prostaglandin f2a or increased local production of substance vasodilators as prostaglandin E2 and prostacyclin.

Other secondary causes responsible are endometrial disease such as endometritis; studies have demonstrated a relationship between histopathologic diagnosis of endometritis and AUB [32].

Endometritis is suspected during hysteroscopy when signs of edema, diffuse endometrial hyperemia, and endometrial polyps less than 1 mm in size are seen.

Confirmation of the diagnosis is by histopathological findings: superficial stromal edema, increased stromal density, and pleomorphic infiltrate dominated by lymphocytes and plasma cells (CD138).

16.9 Iatrogenic (AUB-I)

Medical devices, like LNG-IUS, and even some drugs can cause AUB [33].

Gonadal steroids such as estrogens, progestins, and androgens impact the control of ovarian steroid genesis through effects on the hypothalamus, pituitary, and even ovary itself and also exert a direct effect on the endometrium [34].

Pharmacological agents able to cause AUB are phenothiazines, tricyclic antidepressant, and anticoagulant drugs as low-molecular-weight heparin with similar manifestation to disorders of AUB-C.

The PALM COEIN revision (2018) includes the modem non-vitamin K antagonists such as rivaroxaban that appears to have a greater impact on menstrual bleeding [35].

16.10 Not Yet Classified (AUB-N)

This category is now called "not otherwise classified "and included some uterine entities as uterine arterial-venous malformations [36–38] and the lower segment or upper cervical niche or "isthmocele" frequently after cesarean delivery and sometimes responsible for AUB [39, 40].

Uterine arterial-venous malformations might cause AUB but it is something that wasn't clearly probed due to a lack of well-designed studies.

UAVM are rare. They mostly occur after endometrial trauma or are less often congenital.

When symptomatic they may be a cause of uterine recurrent and massive bleeding.

UAVM are suspected by Doppler US and hysteroscopy; pelvic MRI seems to be also relevant.

Angiography confirms the diagnosis and allows concomitant embolization that seems to be the treatment of choice.

16.11 Summary

Office hysteroscopy is the gold standard for examination of uterine cavity in case of abnormal uterine bleeding.

Vaginoscopy approach, miniaturized instruments, low invasiveness, security, painlessness, and no request of anesthesia or analgesia are the advantages of this technique.

Healthcare professionals should have the necessary skills and expertise to carry out hysteroscopy procedures.

An advantage of the new PALM COIEN classification is an improvement of clinical and scientific perspectives for the study of AUB due to a unification of criteria and its global applicability by clinicians and researchers.

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Hysteroscopy and Infertility

17

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17.1 Introduction

The uterine factor represents an important concern in female infertility with relevant effect on both embryo implantation and placentation processes [1–3]. Indeed, the complex interplay between the embryo and the uterine cavity is an important step during embryo implantation and in the first phases of embryo development [1].

Hysteroscopy is the gold standard for uterine factor evaluation allowing a direct visualization of uterine cavity and in most of the cases an immediate treatment of intrauterine anomalies without hospital admission or anaesthesia [4].

To date, the role of hysteroscopy in the initial evaluation of infertile couples is still under debate. According to NICE and ASRM guidelines, this procedure should not be routinely offered unless clinically indicated considering that less invasive and most costly procedures for the diagnosis of uterine anomalies, such as sonohysterography and hysterosalpingography, are available [5, 6]. On the other hand, it is well recognized that only hysteroscopy represents the definitive method for diagnosis and treatment of uterine pathology [6]. Furthermore, hysteroscopic techniques allow a dramatic reduction of cost and complication related to hospital admission and could guarantee a quick recovery [7]. Finally, the capability "to see and treat" the intrauterine anomalies at the same time offers the unique opportunity to reduce diagnostic workup of infertility and in turn to potentially reduce time to pregnancy [3]. Indeed, the prolonged time to pregnancy is considered as a crucial issue due to the dramatic increase in the mean age of childbearing registered worldwide [8].

A recent systematic review and meta-analysis demonstrated how hysteroscopy could significantly improve IVF outcomes in infertile couples at different stages of their diagnostic–therapeutic workup [3]. In summary, the hysteroscopic removal of intracavitary abnormalities (i.e. endometrial polyps or submucous fibroids) may be beneficial in improving the chance of pregnancy in women with otherwise unexplained subfertility.

Furthermore, there is also evidence that the benefit of hysteroscopy could extend beyond the treatment of intrauterine abnormalities. In detail, a significantly higher pregnancy rate (RR1.45) and live birth rate (RR 1.48) were detected in infertile women without intrauterine pathologies who underwent hysteroscopy prior to IVF compared with no hysteroscopic procedures. These findings could be explained by the beneficial effect exerted by saline irrigation of uterine cavity [9] and facilitation of embryo transfer technique [3]. In addition, the sole hysteroscopy manipulation of the endometrium (hysteroscopy "scratch") might be able to improve endometrial receptivity by modulating the expression of gene encoding implantation-related factors such as glycodelin A, laminin alpha-4, integrin alpha-6, and matrix metalloproteinase-1 [10, 11].

A relevant effect was also observed in those with repetitive implantation failures (RIF) (RR 1.41). Indeed, hysteroscopic evaluation and endometrial scratch represent a valuable option in women with unexplained RIF history (evidence level 1+) [12].

In this chapter, we report a series of successful hysteroscopic management of less common intrauterine anomalies related to infertility.

17.2 Chronic Endometritis

Chronic endometritis is a local inflammatory disorder affecting the endometrium. It is characterized by unusual plasmacyte (PC) infiltration in endometrial stromal areas,

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© Springer Nature Switzerland AG 2020

A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_17

Fig. 17.1 Hysteroscopic view of chronic endometritis: the stromal oedema and micropolyps are clearly evident on the anterior wall

recognized as superficial mucosal oedematous change, elevated stromal cell density, dissociated maturation between epithelial cells and stromal fibroblasts [13, 14]. The prevalence of this condition was reported to be extremely high (≈72%) in women with suspected pelvic inflammatory disease [15]. Due to mild or negligible clinical manifestations, CE is usually ignored by clinicians; however a relevant relation with infertility and neonatal complication is emerging [13]. For instance, histopathologic chronic intervillositis and decidual PC infiltration were associated with several neonatal complications such as preterm labour and neonatal periventricular leukomalacia/cerebral palsy [13, 17]. Moreover, recent studies suggested how chronic endometritis is highly prevalent in patients with unexplained infertility and that CE treatment could significantly improve spontaneous pregnancy rate and live birth rate in these women [17] (Fig. 17.1).

17.3 Adenomyosis

Adenomyosis consists of the presence of endometrial glands and stroma surrounded by hyperplastic smooth muscle within the myometrium. In the *diffuse* form, the endometrial invasion is widely spread and usually leads to increased uterine volume and more bothersome symptoms [18]. In the focal form, the lesion is usually characterized by unique nodular aggregation which could be solid ("classic" adenomyoma) or cystic (adenomyotic cyst) [19]. The incidence of adenomyosis is extremely variant ranging between 5% and 70% because of the lack of widely accepted criteria for histopathological diagnosis [20]. Adenomyosis is usually characterized by pelvic pain and abnormal uterine bleeding but an effect on infertility and ART outcomes was also reported [21, 22]. In detail a recent meta-analysis demonstrated that women with adenomyosis had a 28% reduction in the likelihood of clinical pregnancy compared with unaffected women [22]. Adenomyosis also seems to impact negatively the IVF/ICSI outcome owing to reduced likelihood of clinical pregnancy and implantation, and increased risk of early pregnancy loss. In general, the detrimental effect of adenomyosis on IVF/ICSI outcome appears to be related to both reduced probability of clinical pregnancy and increased risk of early pregnancy loss. There are various possible biological interpretations for this effect, including the chronic inflammatory condition, increased local oestrogen production, utero-tubal dysperistalsis and alterations of adhesion molecules, cell proliferation, apoptosis and free radical metabolism [23].

Hysteroscopy represents a valuable uterine-sparing approach in selected cases of focal or diffuse superficial forms. A treatment of small lesion is also possible during outpatient hysteroscopy without hospital admission (Fig. 17.2a, b).

17.4 Dysmorphic Uterus

The presence of congenital uterine anomalies was associated with abnormal embryo implantation and could interfere with placentation [1, 24]. It was estimated that women with recurrent miscarriage showed a high prevalence of uterine anomalies. The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE), recognizing the clinical significance of female genital anomalies, recently established a common working group under the name *CONUTA (CONgenital UTerine Anomalies)*, with the goal of developing a new updated classification system which is primarily based on the uterine anatomy [25]. Among uterine malformation, Class U1/Dysmorphic Uterus is defined as any uterus having normal uterine outline but with abnormal shape of the uterine cavity excluding septa; Class I is further subdivided into three categories:

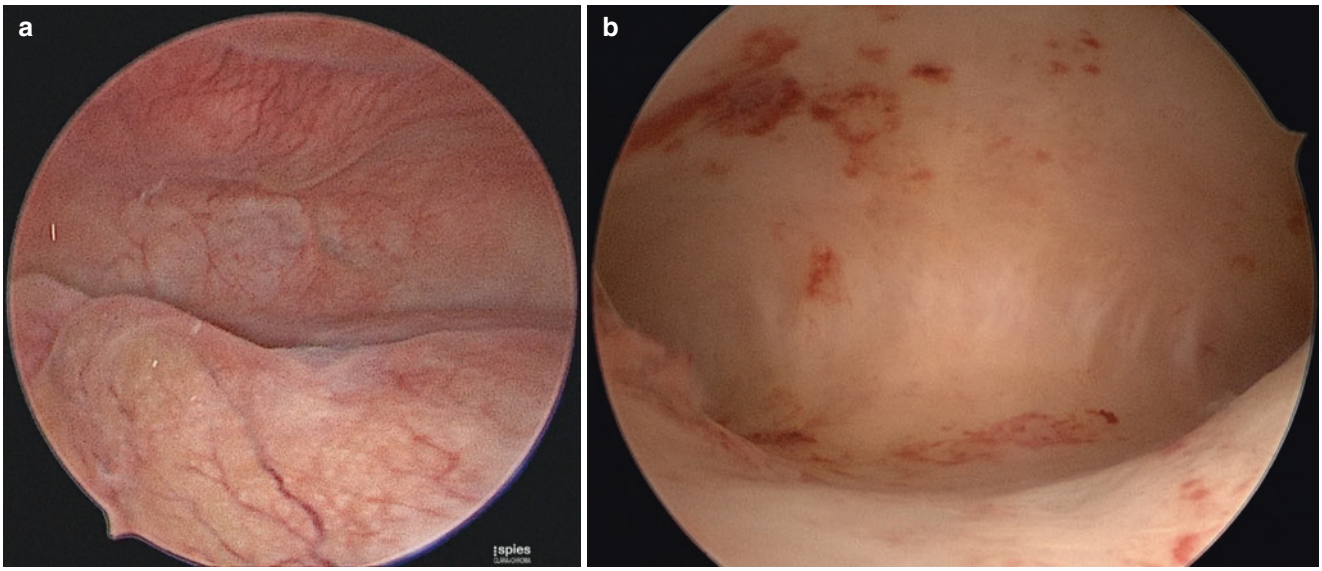

Fig. 17.2 (**a**) Hysteroscopic image suggestive of adenomyosis under hysteroscopic examination performed with a liquid distension medium. The endometrial mucosa of the uterine fundus appears irregular and hyperaemic. (**b**) Hysteroscopic image of the same patient after three cycles of GnRH analogues. Endometrial cavity appears regular and signs of inflammation related to adenomyosis are resolved

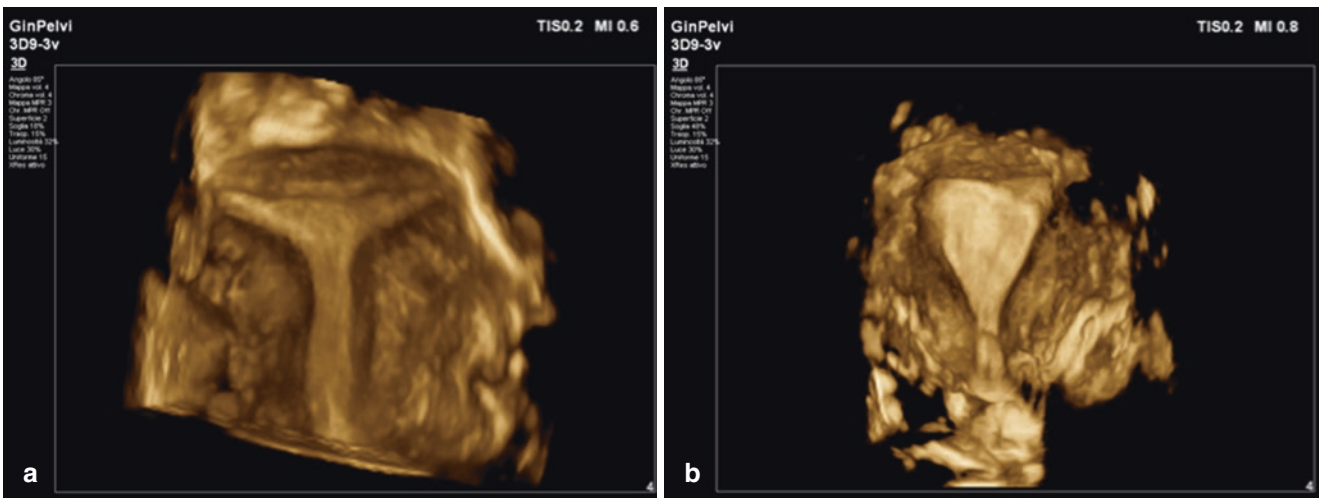

Fig. 17.3 Three-dimensional transvaginal sonography: T-shaped uterus before (**a**) and after (**b**) HOME-DU technique; note the increase in volume and the restored morphology of the uterine cavity

- Class U1a or T-shaped uterus characterized by a narrow uterine cavity due to thickened lateral walls with a correlation 2/3 uterine corpus and 1/3 cervix
- Class U1b or uterus infantilis characterized also by a narrow uterine cavity without lateral wall thickening and an inverse correlation of 1/3 uterine body and 2/3 cervix
- Class U1c or others which are added to include all minor deformities of the uterine cavity including those with an inner indentation at the fundal midline level of <50% of the uterine wall thickness

A Class U1 uterus is associated with poor endometrial receptivity and reproductive outcomes [1, 26]. The hysteroscopic metroplasty improves the spontaneous conception of women with a T-shaped uterus and history of primary infertility [27] (Figs. 17.3a, b and 17.4).

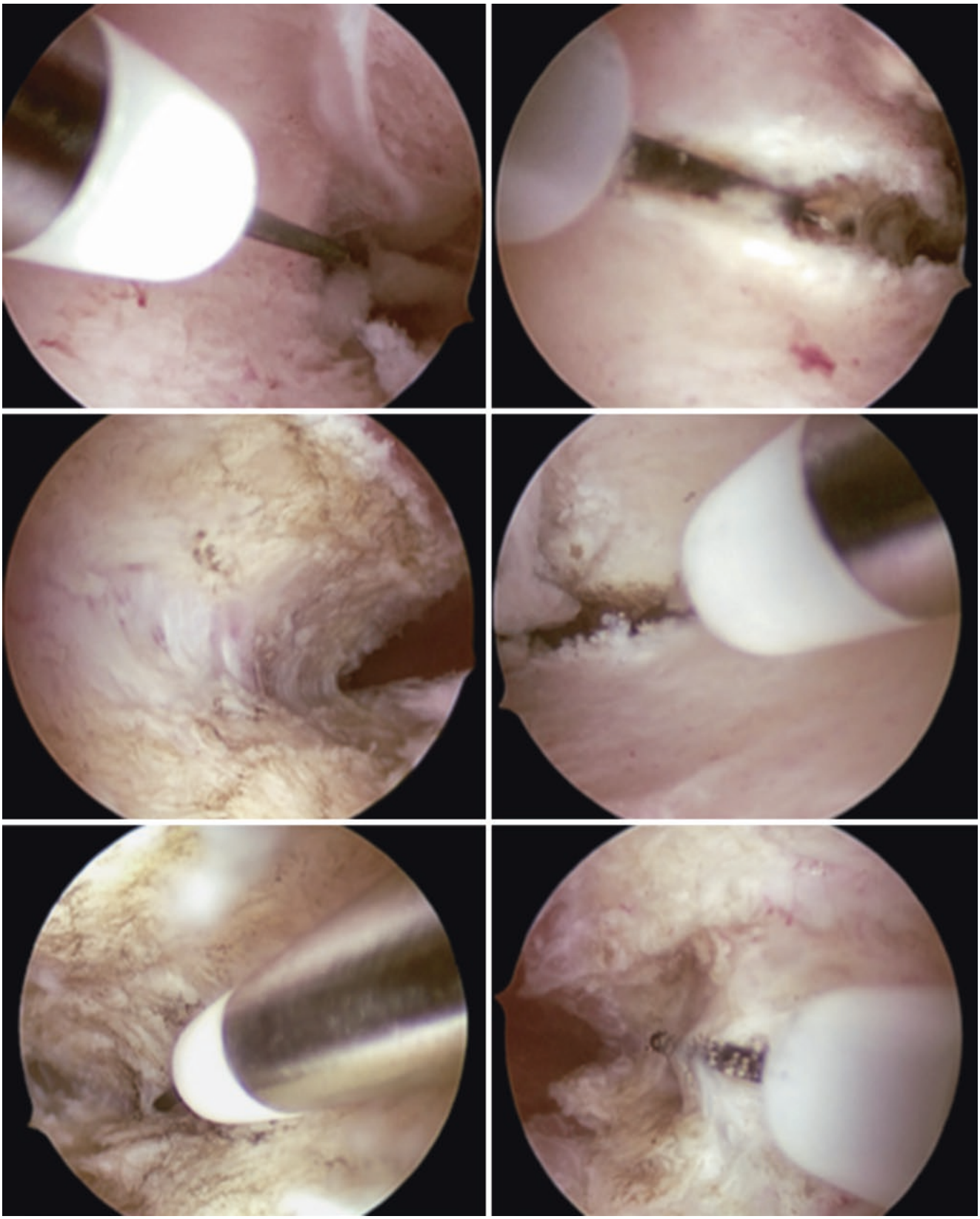

Fig. 17.4 The HOME-DU technique (Hysteroscopic outpatient metroplasty to expand dysmorphic uteri)

17.5 Isthmocele

Isthmocele is a structural anomaly of anterior isthmic wall of the uterus located at the site of a previous caesarean section [28]. The prevalence of clinical symptomatic isthmocele after caesarean is still unknown ranging between 19.4% and 88% [29]. The most common symptoms related to this condition are abnormal bleeding, dysmenorrhoea and dyspareunia [30]. In addition, isthmocele could interfere with mucus quality, sperm migration and embryo implantation leading to secondary infertility [30]. Several surgical approaches have been proposed to treat this condition. To date, the hysteroscopic approach represents a safe and an effective strategy in the management of isthmocele allowing an adequate improvement of symptoms and fertility restoration in most of the cases [31]. This approach is recommended with residual endometrial thickness of at least 3 mm in order to prevent bladder injuries [28] (Figs. 17.5, 17.6 and 17.7a–l).

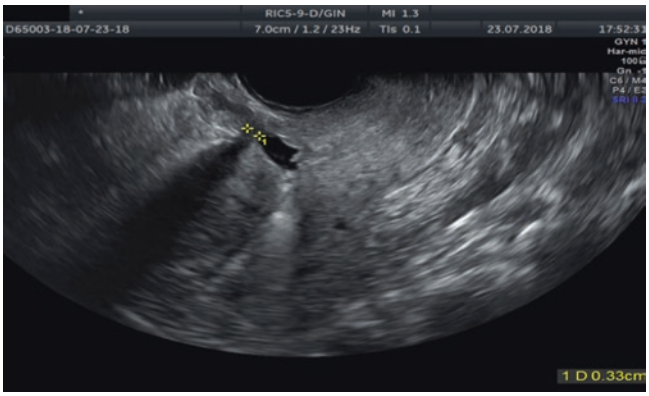

Fig. 17.5 Two-dimensional transvaginal sonography: The sagittal scan of the uterus shows a voluminous anechoic area that interrupts the continuity of the anterior wall of the isthmus and which communicates with the lumen of the cervical canal

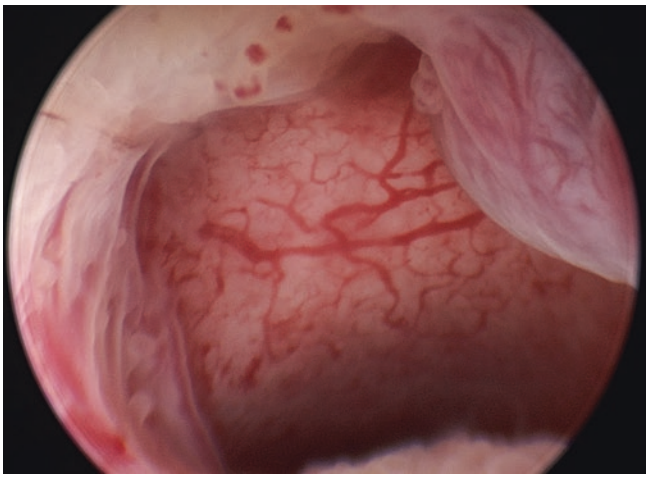

Fig. 17.6 Hysteroscopic view: polyps and pseudopolyps detected in the pouch of an isthmocele, accompanied by pronounced accentuation of the vascular pattern, a stromal oedema and dilated glandular outlets

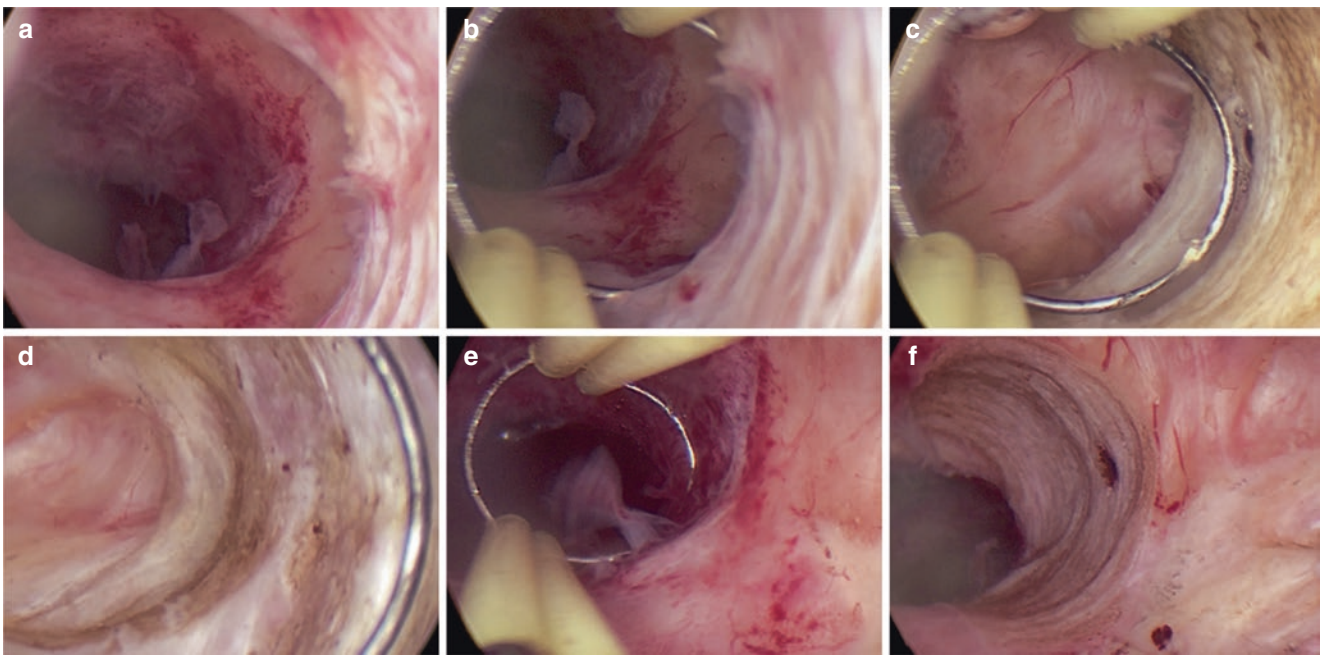

Fig. 17.7 Isthmoplasty technique using a 26Fr bipolar resectoscope (*KARL STORZ, Germany*). The isthmocele is located in the lower segment of the cervical canal, mainly localized in the left anterolateral wall (**a**); a cutting loop is used to even out the pouch by resetting first its interior margins (**b**–**d**) followed by the superior margins of the isthmocele (**e**) until the underlying muscular tissue is reached (**f**); subsequently, the fundus of the pouch is treated using a *ball electrode* to achieve a targeted, focal electro-cauterization of the base of the pouch and resulting in a smooth fundal surface of the isthmocele (**g**, **h**). Similar surgical manoeuvres are performed on the contralateral side (right anterolateral wall) (**i**–**k**) for complete ablation of isthmic region (**l**)

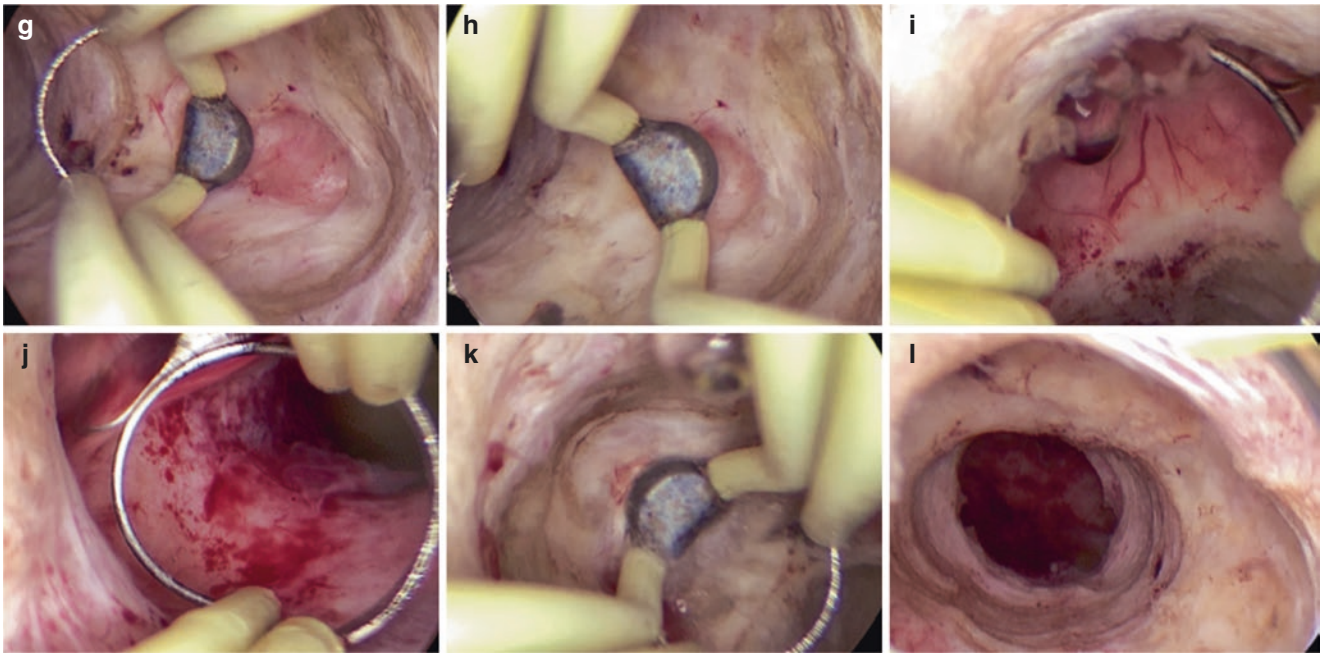

Fig. 17.7 (continued)

17.6 Cases

(a) Chronic endometritis
(b) Adenomyosis
(c) Dysmorphic uterus
(d) Isthmocele

We report cases of a patient with chronic endometritis, adenomyosis, dysmorphic uterus and isthmocele, diagnosed by hysteroscopy.

Case Description on Chronic Endometritis
Relevant anamnestic data: Age 39 years

Clinical history: The patient was referred to us reporting on chronic pelvic pain along with menometrorrhagia that she had been having for 8 months. Her blood count, liver and renal function, and urine test were in normal ranges, except for a mild leucocytosis (13.000/μL). βHCG test was negative.

Gynaecological and obstetric anamnesis: In her obstetric history, she had one vaginal delivery 10 years before and two miscarriages. The patient also complained about secondary infertility: along with her partner, they had been looking for pregnancy for almost 18 months, without any results despite three IVF attempts.

Diagnosis:

Objective examination: Per vaginal examination, we could just notice a significant bleeding, without any other anomalies.

Transvaginal sonography (TVS): Transvaginal ultrasound revealed slightly increased uterine size with dysmorphic echogenic contents in the uterine cavity. Increase in endometrial thickness, asynchronous with the phase of the menstrual cycle.

Hysteroscopy: It was performed in the proliferative phase of the menstrual cycle, and allows to identify endometrial signs of inflammation. All the typical signs were present: hyperaemia stromal oedema and inflammatory micropolyps (<1 mm) (Fig. 17.1).

Material for endometrial culture with a relative antibiogram was obtained. Histopathology revealed chronic endometritis. She was given oral therapy: specific antibiotics along with oral contraceptives. In the following examination, 3 months later, the patient showed an improvement of the symptomatology and the diagnostic hysteroscopy performed showed an almost solved inflammation. Two months after the end of therapy, the patient underwent IVF with positive pregnancy outcome.

Case Description on Adenomyosis
Relevant anamnestic data: Age 32 years

Clinical history: The patient was referred to us reporting on menorrhagia that she had been having for 7–8 years and primary infertility.

General anamnesis: She reported a thalassemia trait, which caused slight-mild anaemia during her life. Her recent blood count showed a severe microcytemic anemia (Hb 7.8 g/dL MCV 71fl).

Gynaecological and obstetric anamnesis: She reported a history of regular menstrual periods, with heavy bleeding and severe dysmenorrhoea; she also reported a laparoscopic surgery for endometriotic cyst almost 6 years before. She assumed progestin-only oral contraceptives to keep endometriosis under control for almost 2 years after the surgery, but then she interrupted to look for maternity.

Along with her partner, they had been looking for pregnancy for almost 3 years, without any results despite ovulation monitoring and two IVF attempts.

Diagnosis:

Objective examination: No abnormalities were diagnosed, except for a little haemorrhagic cystic lesion assuming a dark blue appearance and pain caused by the gynaecological examination.

Transvaginal sonography (TVS): Transvaginal ultrasound revealed that increased uterine size, asymmetry in the thickness and severe inhomogeneity of myometrial walls, poorly defined endometrial-myometrial interface and regular endometrial thickness agree with the menstrual phase. Colour Doppler sonography revealed a rich vascularity that presented an orthogonal orientation in relation to the endometrium and was particularly evident in the inner part of myometrium. No other signs of endometriosis were evident at US pelvic exam.

Hysteroscopy: The endometrial mucosa appears irregular, thick, markedly hyperaemic in the presence of an irregular endometrial vascular network (Fig. 17.2a).

She was admitted to treat the anaemia, complete the diagnosis and decide an appropriated management. Oncological markers were dosed: *Ca125* was mildly increased (54 U/mL). *MRI* was performed and suggested the presence of diffuse adenomyosis without other signs of pelvic endometriosis. The patient was treated with GnRH analogues for 3 months. At follow-up, the clinical status of the patient was improved with much less pelvic pain and menorrhagia; her blood count and haemoglobin rose to normal ranges; the hysteroscopy showed a more regular endometrial surface, without signs of abnormal vascularization and inflammation (Fig. 17.2b). Three months later the patient underwent IVF, with positive results.

Case Description on Dysmorphic Uterus

Here we reported a case of an infertile patient with an history of T-shaped uterus treated with an innovative hysteroscopic technique named hysteroscopic outpatient metroplasty to expand dysmorphic uteri (HOME-DU).

Relevant anamnestic data: Age 28 years

Clinical history: The patient was referred to us complaining about primary infertility. Blood count and liver renal end hormonal exams were in normal ranges.

Gynaecological and obstetric anamnesis: She had menarche at 13 years, and she had regular and normal cycles with mild dysmenorrhea. Karyotype didn't show any anomalies. She had been looking for maternity for almost 18 months, without any results. She did not undergo any medically assisted procreation technique.

Diagnosis:

Objective examination: No abnormalities were diagnosed per speculum and per vaginal examination.

Transvaginal sonography (TVS): Transvaginal ultrasound revealed smaller uterine size. At 3D TVS the endometrial cavity was confirmed anomalous: the lateral angle was <140° and a fundal/corpus-isthmic cavity ratio (W1/W2) was 4.5:1. These results were suggestive for dysmorphic uterus (Fig. 17.3a).

Hysterosalpingography: The fallopian tubes were bilaterally open.

Hysteroscopy: The exam showed an extended intertubal distance in the longitudinal uterine axis and an increased smooth muscle component on the walls of the uterine cavity.

Thanks to a new hysteroscopic technique (HOME-DU) it was possible to improve the volume and the morphology of the uterine cavity. The technique involves two incisions of 3–4 mm in depth made with a 5-Fr bipolar electrode along the lateral walls of the uterine cavity in the isthmic region, followed by additional incisions placed on the anterior and posterior walls of the fundal region up to the isthmus. The operation ends with the application of an anti-adhesive gel (Fig. 17.4). Three months later, at follow-up 3D TVS showed a larger endometrial cavity, with improved lateral angle and a fundal/corpus-isthmic cavity ratio (W1/W2) of 2.8:1 (Fig. 17.3b). Four months after the operative hysteroscopy, the patient was spontaneously pregnant.

Case Description on Dysmorphic Isthmocele

Relevant anamnestic data: Age 38 years

Clinical history: The patient was referred to us complaining about a postmenstrual abnormal uterine bleeding. Blood count and liver renal end hormonal exams were in normal ranges.

Gynaecological and obstetric anamnesis: Karyotype and hysterosalpingography didn't show any anomalies. In her obstetric history, she had a pregnancy complicated by IUGR and hypertension ended with urgent caesarean section.

Afterwards, she had two miscarriages, the latter one 1 year before. The patient complained about secondary infertility: along with her partner, they had been looking for pregnancy for almost 3 years, without any medical assistance.

Diagnosis:

Objective examination: No abnormalities were diagnosed per speculum and per vaginal examination.

Transvaginal sonography (TVS): Transvaginal ultrasound revealed regular uterine size with a grade 2 isthmocele

(area 22 mm^3); the thickness of residual myometrium at the level of the isthmocele was 3.3 mm (Fig. 17.5).

Hysteroscopy: Anatomical defect similar to a pouch was located at the height of the superior third of the anterior wall of the isthmus or cervical canal. Pseudo-polypoid endometrium and typical signs of endometrial inflammation (i.e. "*micropolyps*") were present (Fig. 17.6).

Thanks to the thickness of residual myometrium >3 mm, resectoscopic technique (also termed *isthmoplasty*) was applicable (Fig. 17.7).

She assumed oral contraceptives for 3 months after the hysteroscopic treatment. Ultrasonographic follow-up showed a reduced (almost rectified) difference in level. The patient didn't complain about any abnormal bleeding during the previous months.

Four months after the operative hysteroscopy, the patient was spontaneously pregnant with only help of ovulation monitoring.

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The Role of Hysteroscopy in Diagnosis and Management of Recurrent Pregnancy Loss (RPL)

18

Marco Gergolet and Michael Kamrava

Recurrent pregnancy loss (RPL) or miscarriage (RM) represents a stressful condition for women and their families due to the frustration of repeated achievement of pregnancy with consequent pregnancy loss. Despite the still valid definition of RM, defined as the occurrence of three or more consecutive miscarriages, the American Society for Reproductive Medicine (ASRM) stated in 2008 that the threshold of three miscarriages should be considered only for statistical and epidemiological purposes, whereas diagnostic workup should start after the second pregnancy failure [1, 2].

Although sporadic pregnancy loss occurs in as many as 50% of pregnancies [3], only 5% of couples will be diagnosed with RPL. No cause can be found in approximately 50% of cases of RPL. The causes and workup of RPL differ widely depending on the gestational age of the loss. Thus, it is helpful to consider losses as pre-embryonic ("chemical pregnancy" or anembryonic gestation detected by ultrasound), embryonic (<10 weeks' gestation), or fetal (10 or more weeks' gestation) [4].

There are many possible etiologies for both recurrent and sporadic pregnancy loss. The most common causes of RPL are genetic abnormalities (accounting for >50% of cases). These abnormalities can reflect whole-chromosome abnormalities (trisomy, monosomy, triploidy, etc.); partial-chromosome abnormalities (e.g., macro- and microdeletions and insertions, unbalanced translocations); single-gene disorders affecting exons, introns, and promoter regions; as well as micro-RNA defects and changes in gene function reflecting epigenetic changes.

Another significant cause of recurrent pregnancy loss is due to uterine anomalies whether congenital or acquired [5]. Traditionally surgical corrections have consisted of the use of abdominal or laparoscopic procedures that are associated with increased morbidity and cost to the patients. Development of modern and safer surgical devices has made the use of hysteroscope a cornerstone of diagnosis and treatments in managing patients with recurrent pregnancy loss.

Other less frequent causes of RPL include disorders of thrombosis and hemostasis, immunologic disease, endocrine diseases, infectious etiologies, antiphospholipid syndromes, and other factors including environmental influences such as cigarette smoking [6–9].

18.1 Congenital Uterine Anomalies

According to Venetis congenital uterine anomalies (CUA) represent an increased risk of spontaneous miscarriage (RR 1.68, 95% CI 1.31–2.15) [10]. Saravelos published a review with similar rates of first-trimester miscarriage in all CUA, independently from the type of anomaly [11]. Metroplasty seems to reduce the risk for miscarriage occurrence [10, 12].

Diagnostic hysteroscopy (DH) represents an important tool in the diagnostic workup for RPL, looking for the presence of CUA or acquired anomalies. CUAs are represented by a wide palette of anomalies, which have been reported to cause either primary infertility or RPL. In 2013 a new, simple, and accurate classification of CUA was released by the CONUTA group, an ESHRE-ESGE working group [13]. Subsequently the Thessaloniki ESHRE-ESGE guidelines on the diagnosis of CUA were published. According to the guidelines, DH has the advantage of not only allowing the direct visualization of the uterine cavity but also offering

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_18) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_18

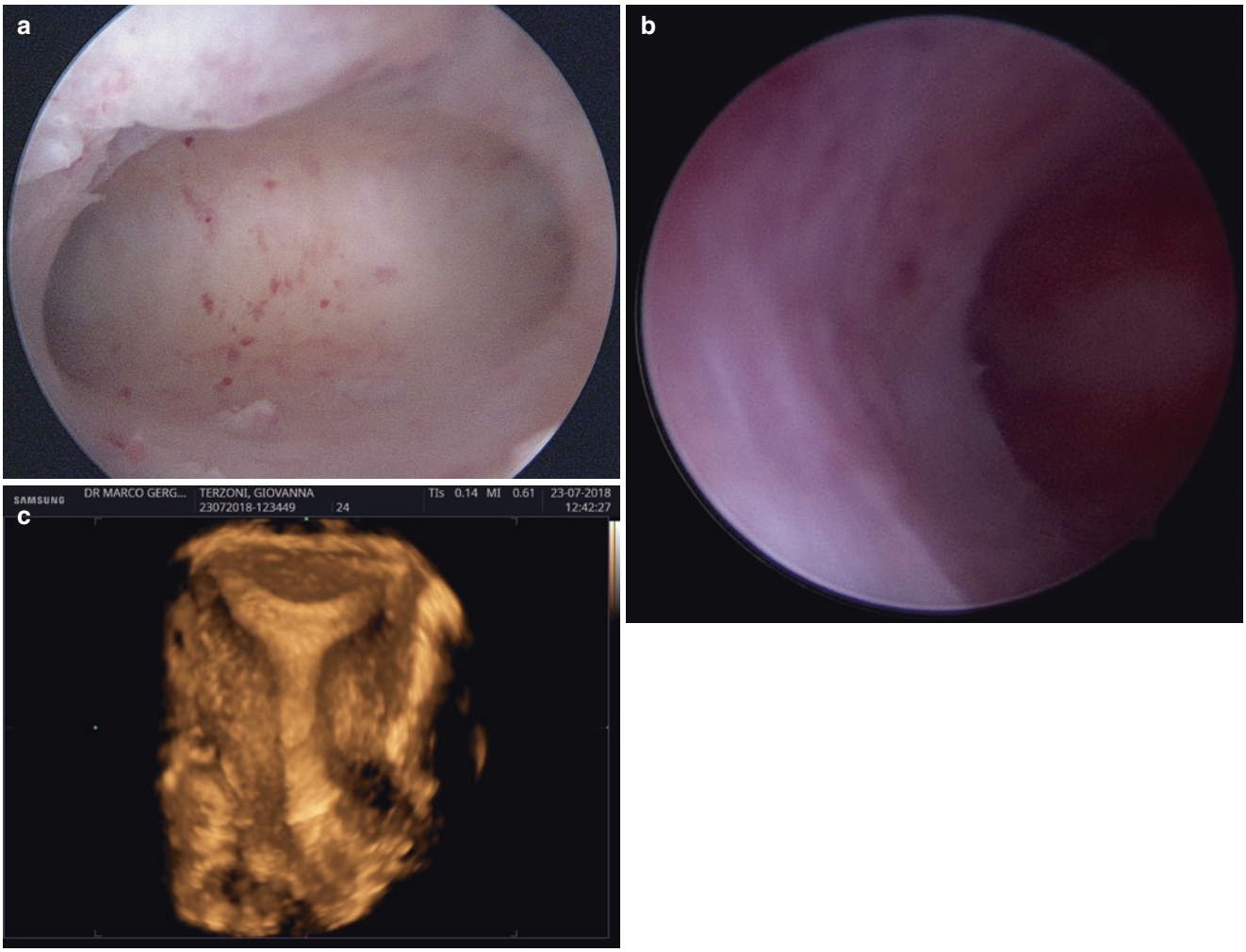


Fig. 18.1 (**a**) T-shaped or dysmorphic uterus (class U1 according to ESHRE/ESGE classification). Small uterine cavity with a minimal indentation of the fundus (bombe). (**b**) From the level of internal uterine orifice the tubal ostia are not visualized. (**c**) 3D US image

the possibility to treat on-site several CUAs such as T-shaped uterus, septate, and bicorporeal septate uterus (see and treat). On the other hand, no information for uterine wall thickness and uterine external contour is available and the differential diagnosis between septate and bicorporeal uterus is difficult or impossible. A combination of 3D volumetric transvaginal ultrasound (TVUS) and office hysteroscopy seems to be the best option for an accurate diagnosis of CUA [14]. Hysteroscopic treatment of CUA mentioned above may be performed either by so-called office scopes, the 5 mm scopes with 5 Fr scissors or bipolar needle through their operative channel using saline solution as distension media, or by resectoscopes. Today there are 15 Fr operative resectoscopes; however there are no data on an advantage in terms of avoiding cervical incompetence using 22 or even 26 Fr scopes. Neither are any data on the advantage of using bipolar instead of monopolar tools in terms of improving fertility outcome. In a prospective study comparing 99 women who underwent metroplasty with 26 Fr resectoscope and 4155 women who delivered in the same hospital authors did not find differences in pregnancy and delivery outcomes [15].

Uterine septums are associated with RM and are easily diagnosed during an office hysteroscopy. When other causes of RPL are excluded and/or treated, a septate uterus may be corrected with a simple hysteroscopic incision or excision [16] (see Figs. 18.1a–c, 18.2a–c, and 18.3a, b and Movies 18.1, 18.2, 18.3, 18.4, and 18.5).

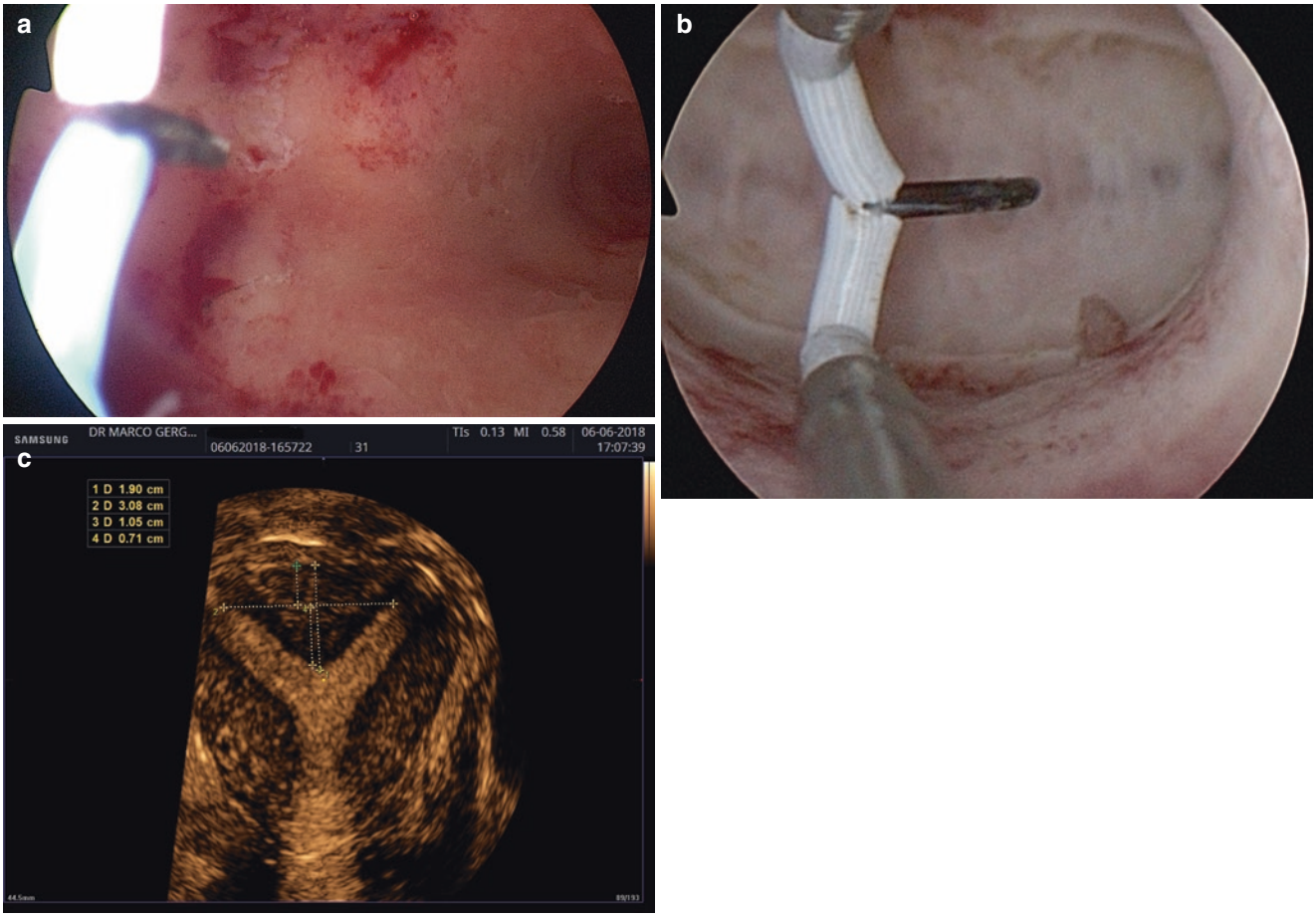


Fig. 18.2 (**a**) Septate uterus U2a (subseptate). According to the definition of the ESHRE/ESGE classification any indentation >50% of the uterine wall thickness is considered septate uterus. The term "arcuate uterus" has been abandoned. (**b**) The uterus after septoplasty. (**c**) The diagnosis at 3D US

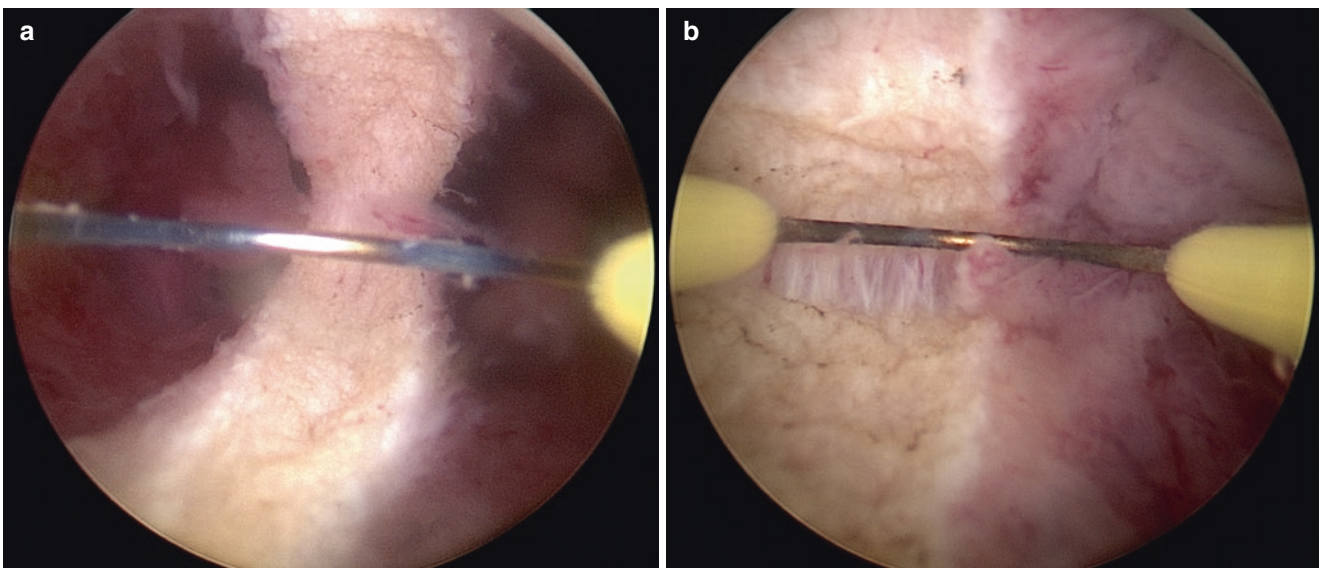


Fig. 18.3 (**a**) Complete septate uterus at the beginning and (**b**) during septoplasty in a patient with a complete septate uterus, double cervix, and longitudinal, nonobstructive, vaginal septum (class: U2bC2V1). (**c**) Ultrasonographic image. See related video of the metroplasty

Fig. 18.3 (continued)

18.2 Acquired Uterine Anomalies

18.2.1 Myomas

According to the literature possible causes of miscarriages are fibroids, adenomyosis, intrauterine adhesions, and polyps. There is substantial evidence in support of uterine cavity-distorting leiomyomas or polyps and RPL [17]. Others have also demonstrated an association between the presence of a uterine septum or bicornuate uterus and RPL [5]. Vaginal sonohysterography, 3D TVUS, and office hysteroscopy are becoming the golden standard in diagnosing these uterine pathologies in the management of RPL.

Submucosal fibroids are divided into three types. Type 0 are completely intracavitary (often described as "intracavitary myomas" rather than submucosal to distinguish them from other submucosal myomas that are partially or almost completely intramural). Type I fibroids have an intramural component, but >50% of the fibroid is located within the endometrial cavity. Type II fibroids also have an intramural component, but <50% is intracavitary. Intramural (IM) fibroids do not distort the endometrial cavity and have <50% of their mass protruding through the serosa. Fibroids extending >50% out of the serosal surface are considered subserosal.

Many hypotheses have been proposed to explain the mechanisms by which fibroids affect fertility. Some of these theories include a reduction in perfusion of the endometrium [18], local inflammatory changes that inhibit implantation, and alterations in normal uterine contractility that limit gamete and embryo migration. However, fibroids alone are often not the only identifiable cause of infertility. Indeed, one recent analysis suggested that when all other causes of infertility are excluded, fibroids are found in only 1–2% of remaining patients.

Furthermore, many patients with fibroids achieve pregnancy without difficulty. Thus, counselling an individual patient about how her fibroids may affect reproduction can be challenging. The literature, however, does provide clear answers in some clinical scenarios. An abundance of data demonstrate that patients with submucosal myomas are less likely to become pregnant and more likely to experience spontaneous abortion than are women who have intramural or subserosal fibroids [17]. Conversely, many studies have demonstrated that patients with subserosal fibroids are not at increased risk of infertility or pregnancy loss. Controversy still exists, however, regarding the effect on fertility of intramural myomas that have no impact on the uterine cavity but cause a distortion of JZ. The majority of studies comparing patients with intramural fibroids and those without fibroids have demonstrated no difference in pregnancy rates. However, in a recent retrospective observational study, patients with non-cavity-distorting intramural fibroids were less likely to become pregnant and more likely to miscarry [19]. Future randomized controlled trials are required to address the role of surgical interventions in patients with intramural and subserosal fibroids before undergoing fertility treatment.

Improved instruments and techniques have made hysteroscopic myomectomy rather than abdominal or laparoscopic procedures a mainstay procedure in the treatment of intrauterine fibroids as a contributing factor in causing RM. In a prospective study hysteroscopic myomectomy improved the chances of pregnancy over no treatment (43% vs. 27%, $P < 0.05$) in patients with submucosal myomas (Movie 18.6).

Diagnostic techniques such as 3D TVUS and MRI allow the visualization of the junctional zone (JZ) or inner myometrium as it seems that the distortion of the JZ has a clinical implication in the presence of intramural myomas [20].

18.2.2 Adenomyosis

Adenomyosis has been reported to have a clinical implication on RPL [21]. The first TVUS sign of this pathology is the thickening of the JZ. In fact, at least at the beginning is pathology of the subendometrium. Here are particular hysteroscopic signs for adenomyosis such as subendometrial cysts, mucosal elevation, and mucosal defects. Performing the exploration of the subendometrium with 5 Fr scissors helps to open the cyst, which contains endometriotic "chocolate" liquid whereas the epithelium covering the cyst is typically endometriotic. Just as adenomyosis, endometriosis seems to be an independent factor for RPL, but in a retrospective study either the group with septate uterus without endometriosis or that with stage I and II endometriosis did not show any clinical difference. The conclusion was that endometriosis could be an occasional finding not influencing the pregnancy outcome [22] (Fig. 18.4 and Movie 18.7).

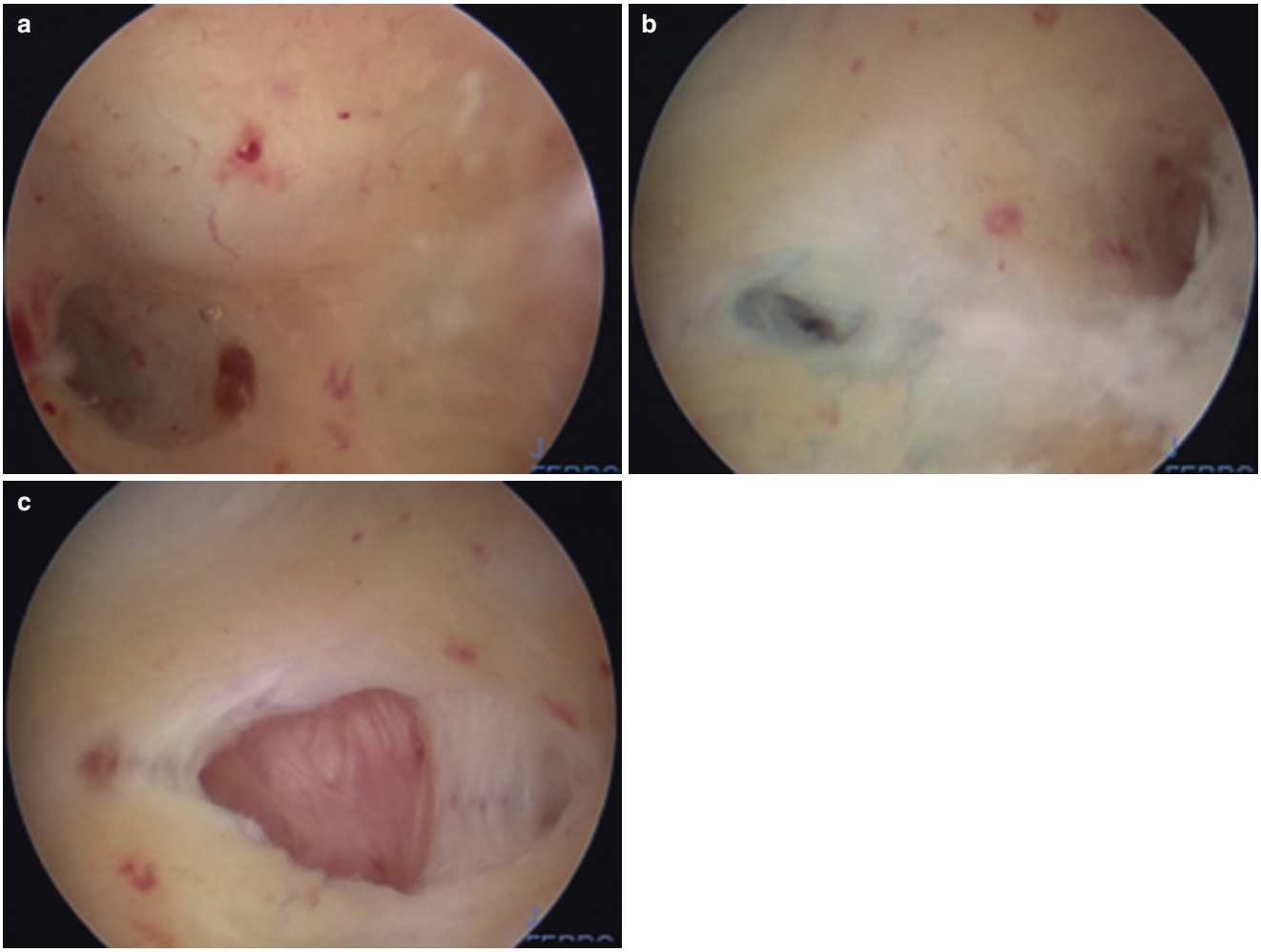


Fig. 18.4 Subendometrial adenomyotic cyst. Adenomyosis may represent a cause for recurrent miscarriage. (**a**) Subendometrial cyst covered by endometrium, (**b**) immediately after opening and (**c**) the aspect of enucleation (courtesy of J. Ferro, Valencia)

18.2.3 Retained Products of Conception

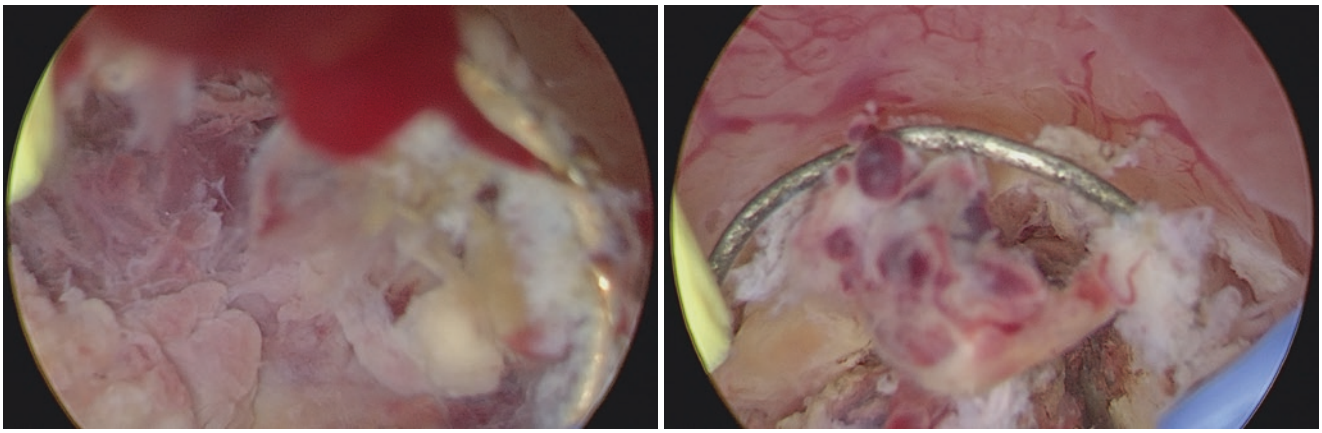
Retained products of conception (RPC) with or without subsequent intrauterine adhesions (IUA) are associated with an increased risk of recurrent miscarriages [23]. Hysteroscopic removal of RPC with cold loop, avoiding as much as possible the use of electricity, seems to be preferable to dilatation and curettage in order to avoid subsequent IUA [24] (Figs. 18.5 and 18.6).

18.2.4 Intrauterine Adhesions and Polyps

The clinical management of pregnancy-loss patients with intrauterine synechiae and uterine polyps is also controversial, and there is no conclusive evidence that surgical treatment reduces the risk of pregnancy loss. However, the general consensus is that in the presence of significant uterine cavity defects, or Asherman syndrome, surgical correction should be considered. In a series of 200 patients with three or more miscarriages, synechiae were present in 12.5%, whereas endometrial polyps in 8.5% of the examined women [25] (Fig. 18.7, Movies 18.8 and 18.9).

18.2.5 Chronic Endometritis

The link between chronic endometritis and RM is not well established despite several papers alluding to an association between the two subject matters. However, when chronic endometritis is treated with appropriate antibiotics against the offending microorganism, successful pregnancies from IVF are much enhanced [26] (Fig. 18.8).



Figs. 18.5 and 18.6 Retained products of conception. Removal of such tissue may be performed using cold loop and limiting electric energy only in case of presence of vessels

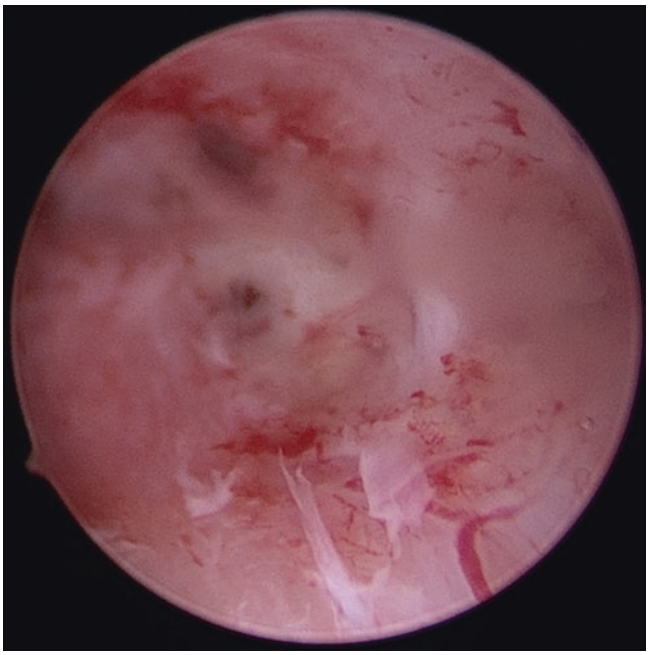


Fig. 18.7 Fibrotic tissue covering the tubal ostium in a patient with secondary infertility

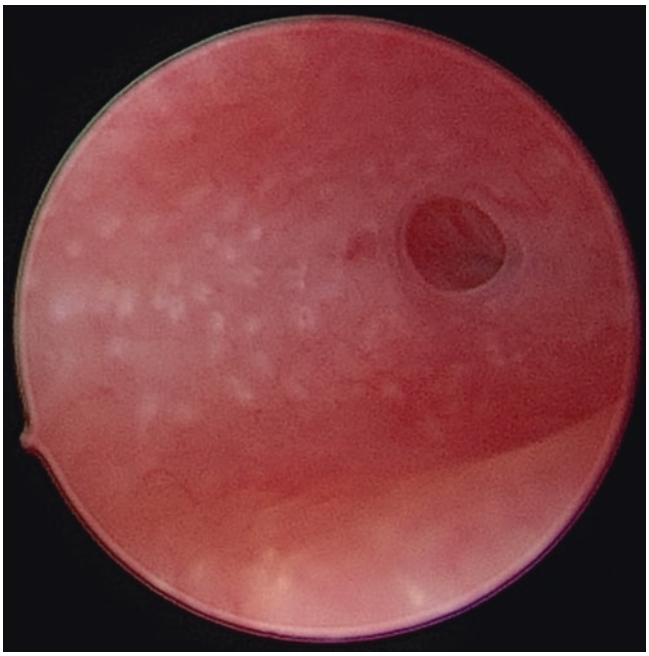


Fig. 18.8 Strawberry pattern, a sign for possible chronic endometritis

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Hysteroscopy During Menopause

19

Jose Carugno and Antonio Simone Laganà

Natural menopause is defined as permanent cessation of menstrual periods, determined retrospectively after 12 months of amenorrhea. It occurs at a median age of 51 years [1] alongside the physiological process of ageing, although women can undergo menopause at an earlier age for medical conditions or after surgery (surgical menopause). Among the clinical conditions associated with early-onset menopause, premature ovarian failure (POF) is defined by the cessation of the ovarian function before the age of 40 [2] and could be caused by autoimmune disorders, thyroid disease, diabetes mellitus, chemotherapy, being a carrier of the fragile X syndrome gene, and radiotherapy among other conditions [3], or the cause could be undetermined (idiopathic). Conversely, surgical menopause is defined by the removal of the ovaries, with or without the removal of the uterus and fallopian tubes. Besides these scenarios, functional disorders of the female reproductive system, such as endometriosis [4] and polycystic ovary syndrome (PCOS), and several other conditions such as cigarette smoking, obesity, racial and ethnic factors, and chronic illnesses may all play a significant role in the menopausal process.

Regardless of the cause(s) of menopause, the process is characterized by a significant decrease of estrogen and progesterone production and, to a lesser extent, also of androgens (especially testosterone, dehydroepiandrosterone-sulfate, and androstenedione). In case of physiologic menopause or POF, the main cause of this transition is the natural depletion and ageing of the oocytes (ovarian reserve); as a consequence, the depletion of the ovarian reserve causes an increase in circulating follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, as a consequence of having fewer oocytes and follicles responding to these hormones and producing estrogen (lack of negative feedback with the hypophysis and hypothalamus). In case of surgical menopause, there is a similar underlining endocrine mechanism, but it occurs in a more expedited fashion. Although sexual hormone production is significantly decreased after menopause, a limited amount of androgens are converted in estrogens by aromatase in the peripheral tissue.

Hot flashes and other vasomotor symptoms are also an important part of the menopausal transition, whereas long-term effects may include osteoporosis, vaginal atrophy, as well as changes of the metabolic profile resulting in cardiac risks [5].

Due to reduced estrogen and progesterone levels, reproductive organs undergo a progressive process of atrophy [6, 7]. This reflects also at the endometrial level: without the cyclic hormonal actions of menstrual cycle, the endometrium in menopause becomes atrophic (Fig. 19.1a–e).

Nevertheless, other intrauterine pathologies, such as endometrial (Fig. 19.2a–c) or cervical polyps (Fig. 19.3a–e and Video 19.1), submucous myomas (Fig. 19.4a, b), and untreated complete/incomplete septa (Fig. 19.5), may also be diagnosed during menopause. In addition, the possibility offered by hormone replacement therapy could modify the endometrium (Fig. 19.6a, b), which may proliferate under hormonal stimuli [8].

Considering amenorrhea and endometrial atrophy as the physiologic consequences of menopause, postmenopausal women are usually referred for diagnostic hysteroscopy due to increased endometrial thickness and/or vaginal bleeding (postmenopausal bleeding, PMB). In this regard, a recent cross-sectional study [9] included 110 postmenopausal women aged 40–82 years who underwent diagnostic

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_19) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_19

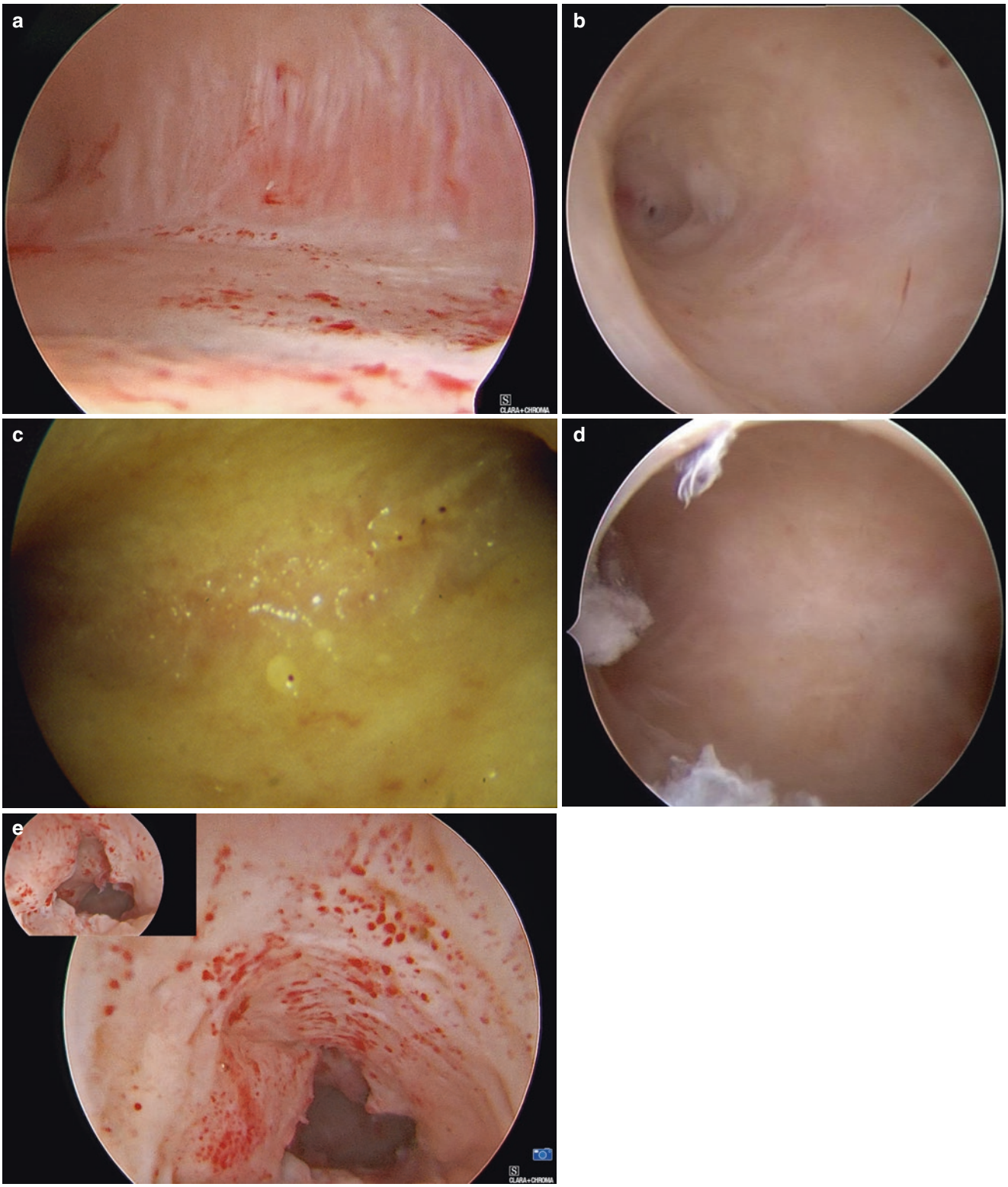

Fig. 19.1 Atrophic endometrium. (**a**) Panoramic view of atrophic endometrial cavity. Appreciate the petechiae on the endometrium of the posterior uterine wall. (**b**) (Image courtesy of Dr. A. Ubeda). Atrophic endometrium. Note the pinpoint tubal ostium. (**c**) (Image courtesy of Dr. A. Ubeda). Panoramic view of atrophic endometrium using CO_2 gas as distention media. (**d**) (Image courtesy of Dr. A. Ubeda). Appreciate the complete atrophy of the endometrial lining in this postmenopausal patient presenting with PMB. (**e**) Atrophic endocervical canal in a postmenopausal patient. Also note the multiple petechiae along the cervical canal

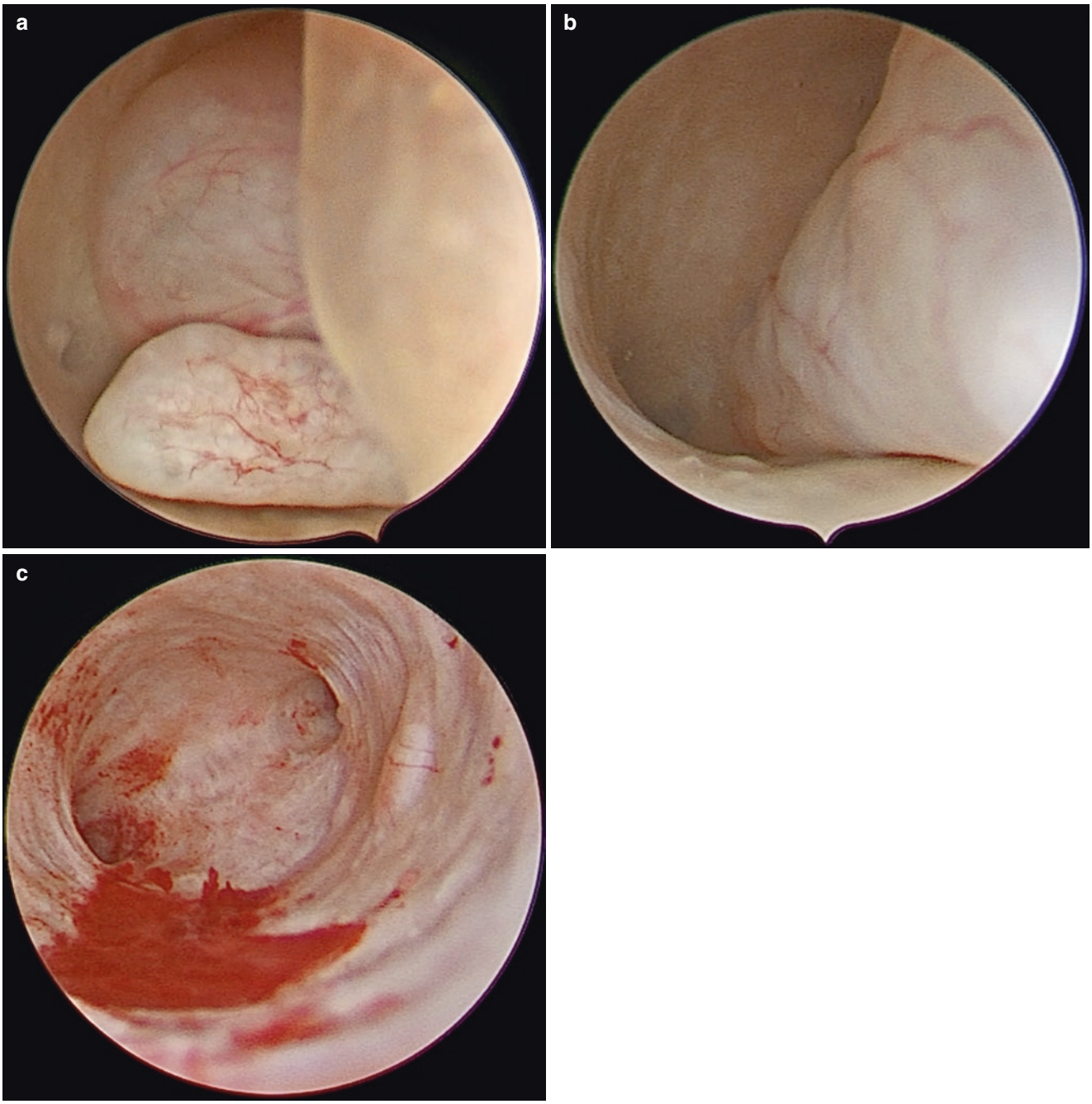

Fig. 19.2 Endometrial polyps. (**a**) Multiple endometrial polyps in a base of atrophic endometrium. (**b**) Large endometrial polyp in a postmenopausal patient. (**c**) Endometrial cavity after polypectomy of the large endometrial polyp. Appreciate the atrophic endometrium and the implantation site of the polyp

hysteroscopy, subdividing them into two groups: 67 women with PMB (PMB group) and 43 asymptomatic women with increased endometrial thickness (asymptomatic group). Researchers found in the PMB group that sensitivity, specificity, and positive and negative predictive values of hysteroscopy for normal findings were 98%, 100%, 100%, and 90%, respectively, in contrast to 98%, 100%, 100%, and 85%, respectively, for the same parameters in the asymptomatic group. Interestingly, the sensitivity, specificity, and positive and negative predictive values of hysteroscopy for polyps and myomas were 100% in postmenopausal women, regardless of the presence of

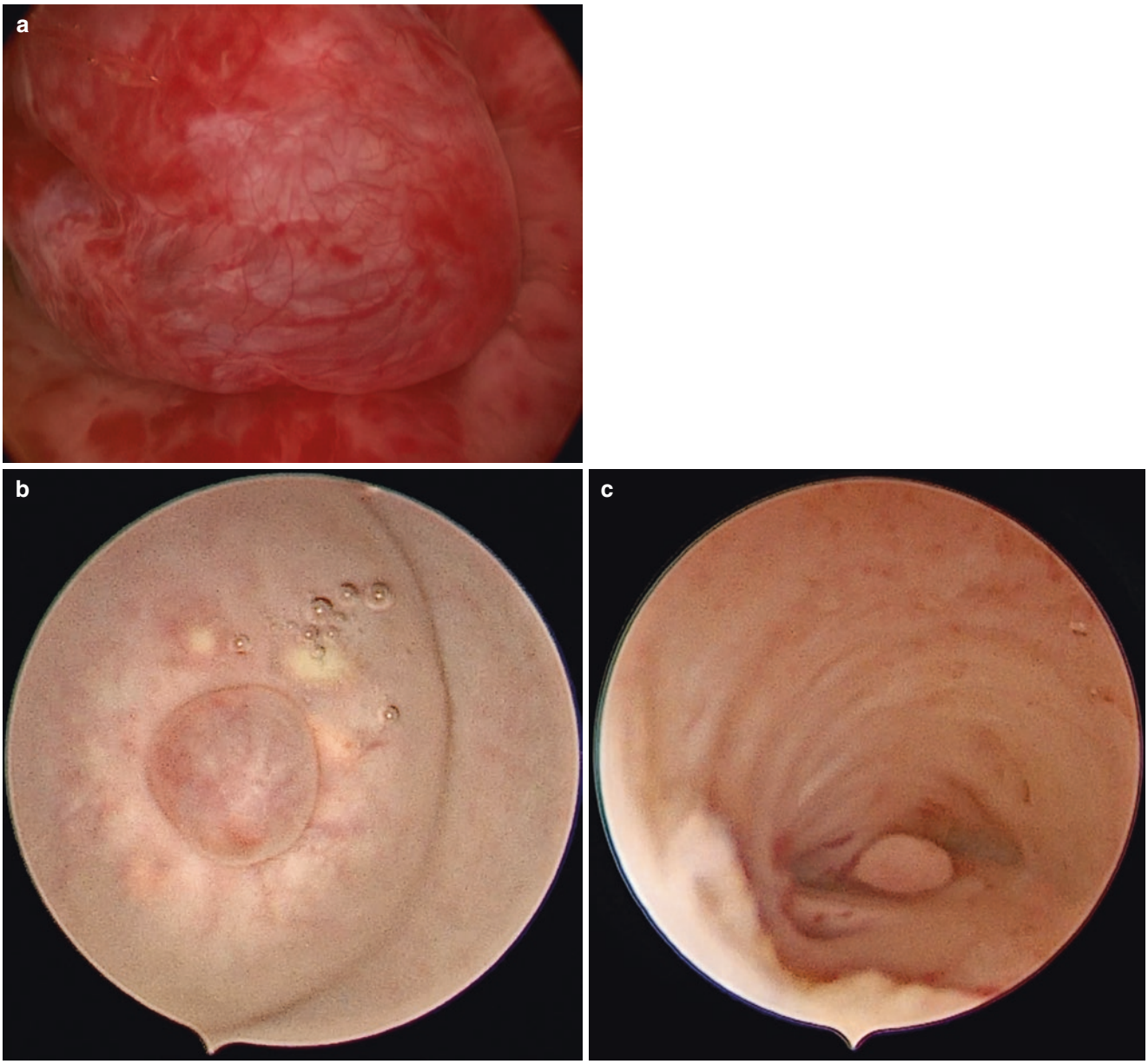

Fig. 19.3 Cervical polyps. (**a**) (Image courtesy of Dr. Medvediev) Large cervical polyp protruding from the external os. Appreciate the vascularization of the polyp. (**b**) Small cervical polyp in a postmenopausal woman seen during vaginoscopy. The external os is not visible due to the size of the protruding cervical polyp. (**c**) Video illustrating a diagnostic in office hysteroscopy in a patient with cervical polyp and multiple endometrial polyps

PMB. Thus, although endometrial thickness in postmenopausal women with or without PMB is frequently due to benign lesions such as polyps and submucosal myomas, these lesions may carry unsuspected malignancies (Fig. 19.7a–d).

In this regard, a recent single-center retrospective study [10] estimated the prevalence of benign/malignant lesions in 631 postmenopausal women undergoing hysteroscopic polypectomy; among them, 30 presented a malignant disorder (4.75%); 579 patients (91.76%) were diagnosed with a simple polyp, 11 with non-atypical simple hyperplasia (1.74%), and 11 with non-atypical complex hyperplasia (1.74%). On univariate analysis age alone proved to be statistically significant (OR = 1.05; 95% CI = [1.02–1.09] $p < 0.01$), with a threshold of 59 years of age on the ROC curve. On multivariate analysis, factors predictive of a malignant lesion were age (OR = 1.06; 95% CI [1.02–1.10]), presence of PMB (OR = 2.4; 95% CI [1.07–5.42]), and family history of endometrial cancer (OR = 2.88; 95% CI [1.08–7.67]). Interestingly, neither the univariate nor the

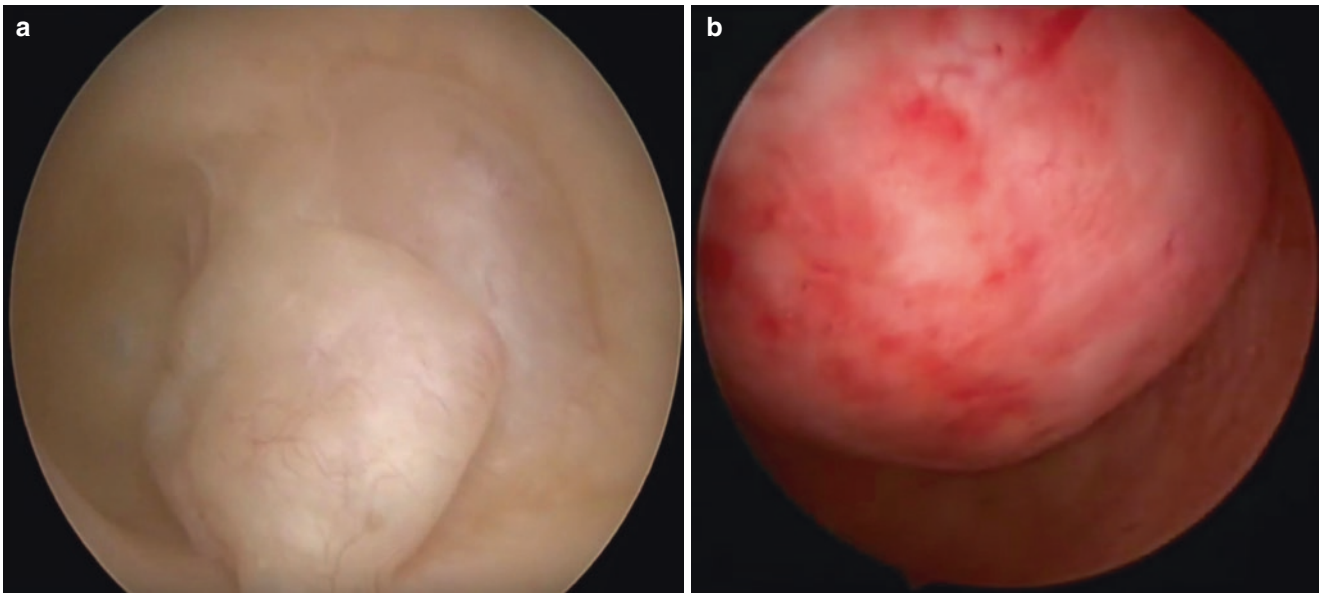

Fig. 19.4 Submucous myoma. (**a**) Type 0 submucous myoma with a thin stalk in a postmenopausal patient. (**b**) Large type 1 submucous myoma

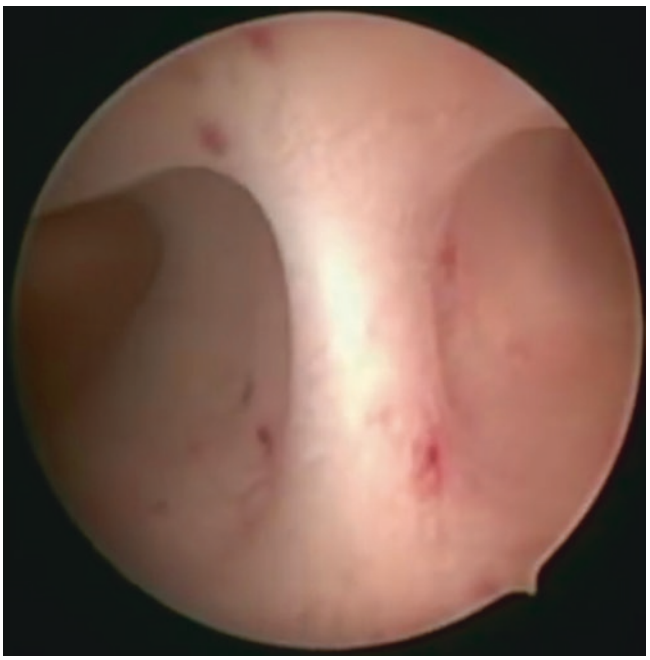

Fig. 19.5 Uterine septa. Uterine septa in a patient who presented with postmenopausal bleeding

multivariate model were able to demonstrate a statistically significant relationship with respect to endometrial thickness. On that basis, another study aimed to determine whether symptomatic endometrial polyps have a genetic phenotype similar to that of endometrial cancer, evaluating the expression of four genetic markers (PTEN, BCL2, MLH1, and CTNNB1), linked to endometrial carcinogenesis, in endometrial polyps of patients with and without PMB. Surprisingly, this study failed to find statistical differences between the two groups regarding the expression of the studied endometrial cancer risk factor genes, or other clinical aspects (duration of menopause, polyp size, presence of systemic hypertension, diabetes mellitus, and smoking habits).

Similar to what happens at the endometrial level, most of the myomas undergo a process of atrophy during menopause, due to reduced production of sexual hormones [11]. Accumulating evidence from semiquantitative immunohistochemistry investigations suggests that the expression of NF-B, interleukin-1β (IL-1β), tumor necrosis factor a (TNF-α), cyclooxygenase 2 (COX-2), and inducible nitric oxide synthase (iNOS) in uterine myomas is significantly affected by ageing and remains higher than in control normal myometrium both in pre- and postmenopause [12]. Nevertheless, myomas express high levels of aromatase known to enhance local pro-estrogenic microenvironment [13] and, in this way, keep their volume steady even after menopause. In any case, ultrasound evaluation should be performed in case of rapid volume growth [14], followed by hysteroscopic biopsy in case of submucous myomas, in order to exclude the rare occurrence of leiomyosarcoma [15].

In case of suspected malignancies, the most relevant symptom in menopausal women is uterine bleeding. According to epidemiological data [16], close to 10% of women with postmenopausal bleeding have endometrial cancer. In 2010, Timmermans et al. [17] performed a systematic review and meta-analysis of individual patient data; they found a comparable receiver operator characteristic (ROC) curves with area under the ROC curve (AUCs) varying between 0.82 and 0.84, allowing to speculate that previous

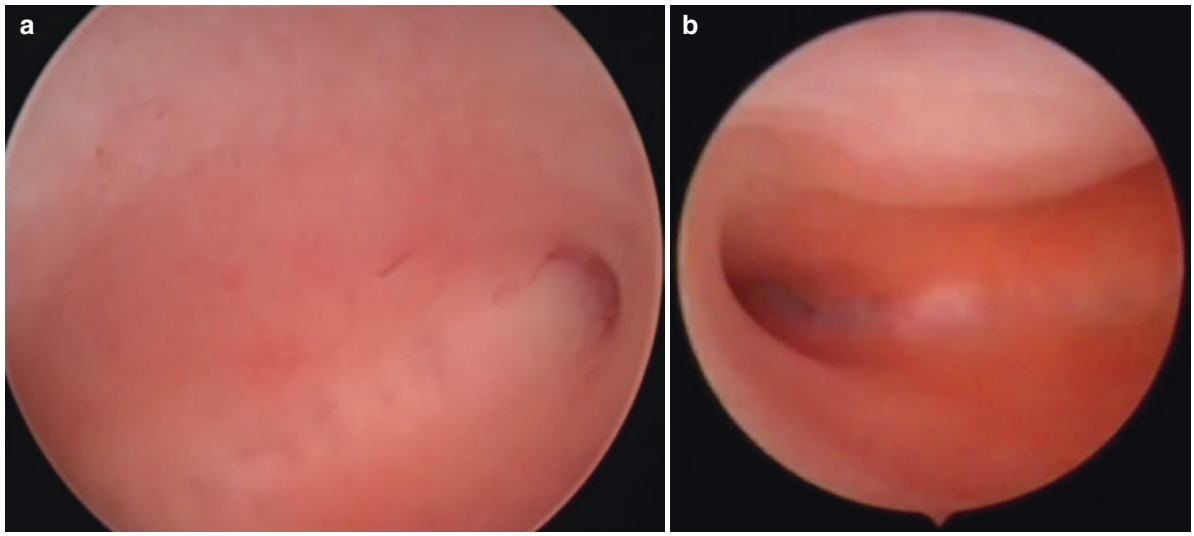

Fig. 19.6 Uterus with HRT. (**a**) Uterus with the effect of HRT on the endometrium. (**b**) Uterus with HRT influence on the endometrium (prior to Fig. 19.9)

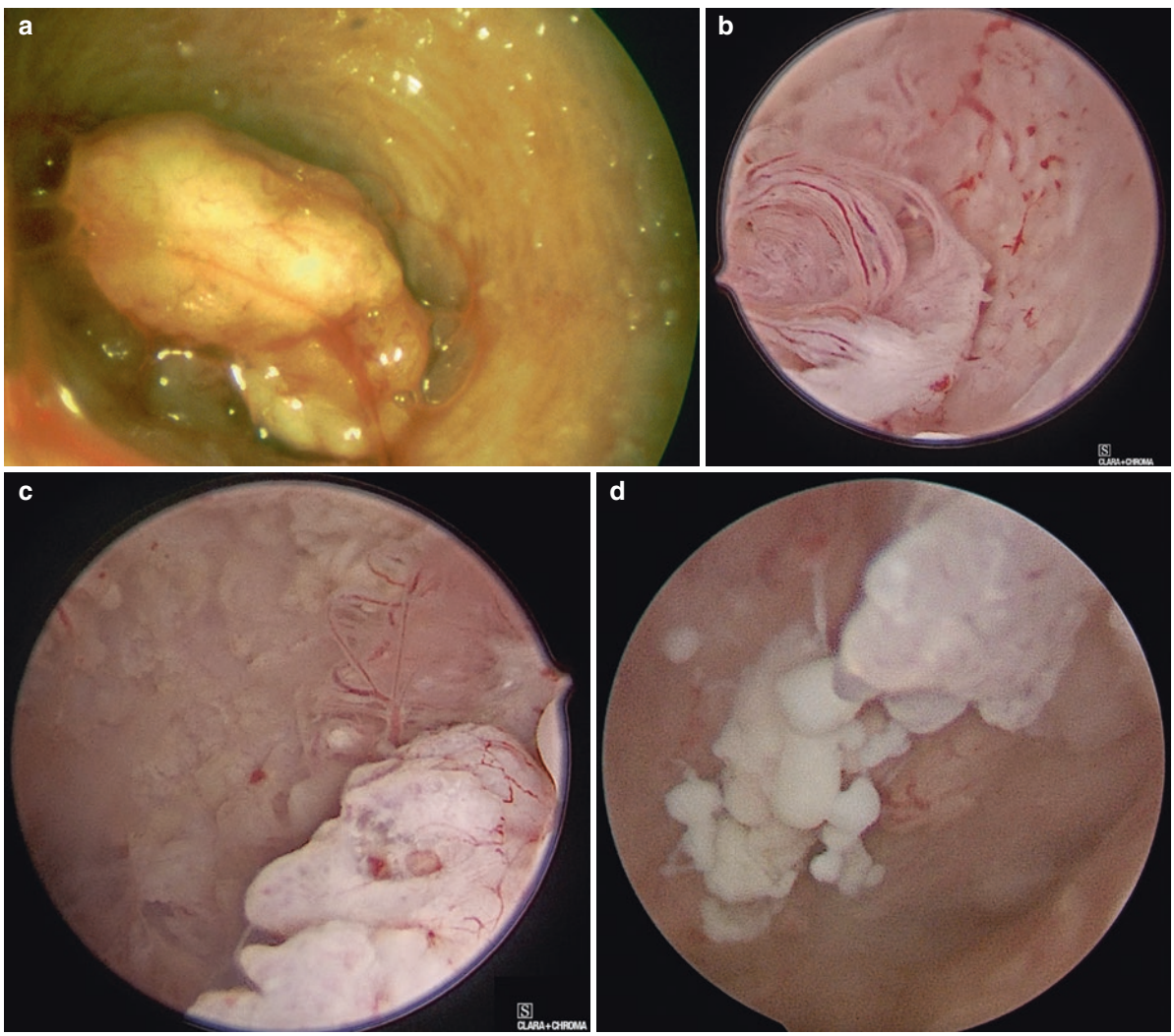

Fig. 19.7 Postmenopausal findings and malignancy. (**a**) (Ubeda) Atrophic endometrium with cornual endometrial cancer using CO_2 as distention media. (**b**) Endometrial cancer in a postmenopausal patient. (**c**) Endometrial cancer. (**d**) Endometrial cancer

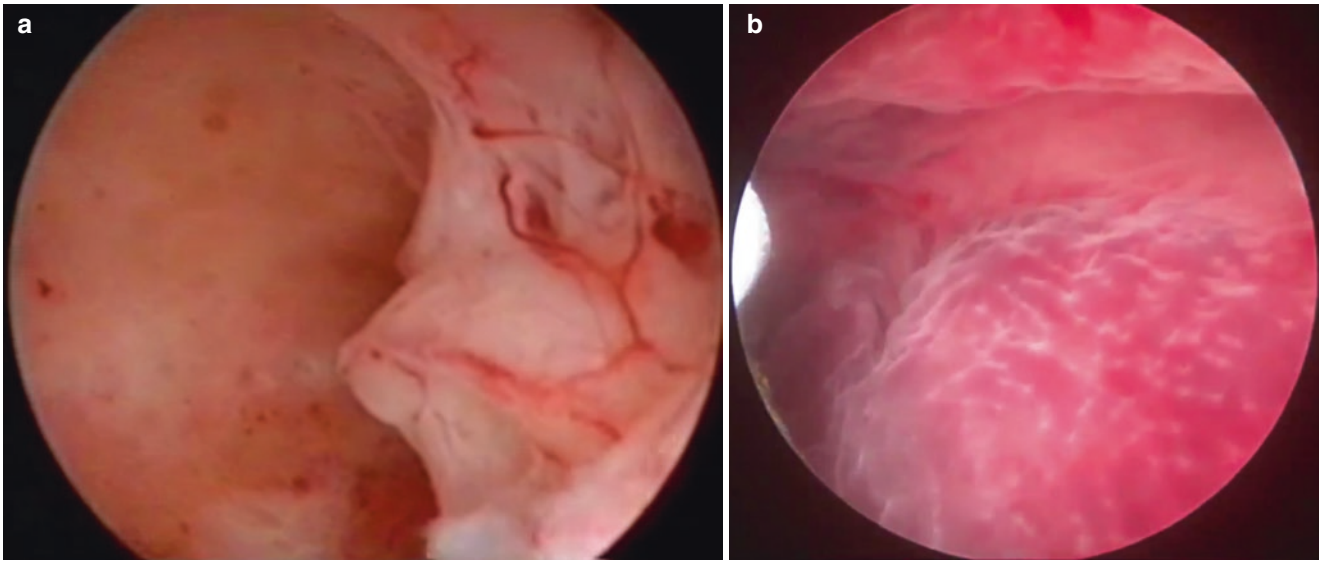

Fig. 19.8 Endometrial hyperplasia. (**a**) Endometrial hyperplasia with atypia. Note the fluffy aspect of the endometrial surface as well as the enlarged vessels. (**b**) Endometrial hyperplasia without atypia

meta-analyses on endometrial thickness measurement have overestimated its diagnostic accuracy in the detection of endometrial carcinoma. Based on these results, they suggest the use of a cutoff of 3 mm of endometrial thickness on vaginal ultrasound for exclusion of endometrial carcinoma in women with PMB. Nevertheless, diagnostic hysteroscopy and endometrial biopsy under direct vision could be considered mandatory in patients presenting with postmenopausal bleeding, regardless of the presence of risk factors for endometrial cancer. In this regard, robust data clearly revealed that hysteroscopy with directed biopsy is more sensitive in detecting all types of uterine lesions than blind dilatation and curettage (D&C). In addition, blind sharp curettage done after hysteroscopy and directed biopsy does not improve the detection of endometrial cancer [18].

In case of asymptomatic postmenopausal women (in the absence of PMB), transvaginal ultrasound measurement of endometrial thickness has low diagnostic potential. According to recent data [19] using ≥4 mm as cutoff, AUC was 0.52 (95% CI 0.44–0.57) which indicated poor accuracy of endometrial thickness of TVUS for the diagnosis of carcinoma conditions (endometrial hyperplasia with atypia and endometrial carcinoma) (Fig. 19.8a, b).

Another concern in postmenopausal women is the presence of vaginal bleeding in the patient receiving hormone replacement therapy (HRT), which is known to stimulate endometrial proliferation to a lesser extent than physiologic hormonal stimuli during reproductive age. Recently, Burbos et al. [19] published a large cross-sectional study of 4847 consecutive women investigated for postmenopausal vaginal bleeding, of which 4097 (84.5%) did not use any HRT at the time of initial referral and 750 (15.5%) were using combined HRT preparations. Interestingly, women using HRT preparations were significantly less likely to be diagnosed with endometrial cancer compared with women not using HRT (adjusted odds ratio = 0.229, 95% CI 0.116–0.452; $P < 0.0001$).

Another drug which may induce endometrial proliferation during menopause resulting in PMB is tamoxifen, usually administered at 20 mg/day in the presence of estrogen-sensitive breast cancer diagnosis. In this regard, hysteroscopy-guided endometrial biopsy is considered the gold standard to exclude malignancies or hyperplasia. In a recent study [20], the most common hysteroscopic and histologic findings in postmenopausal women taking tamoxifen for breast cancer were endometrial polyps (32.5%) (Fig. 19.9) and atrophic endometrium (22.5%). Interestingly, endometrial polyps and polyps associated with atrophic endometrium were estrogen receptor (ER) positive ($p = 0.019$); conversely, polyps that were ER negative were more frequent in patients with atrophic endometrium ($p = 0.01$), suggesting a key role of ER in modulating endometrial proliferation during tamoxifen therapy. Regarding the ideal cutoff in this population to recommend hysteroscopy, although some authors suggested to set it at 8 mm, we believe that it is more appropriate and cautionary to set it at 5 mm [8]. In any case, we should consider that no single ultrasonographic feature (echotexture and borders) is significantly associated with the detection of endometrial hyperplasia or carcinoma. For this reason hysteroscopy, although not predictive unless revealing a focal lesion, is more accurate in detecting polyps and hyperplastic changes [21].

Finally, hysteroscopy play a pivotal role in the evaluation of the vaginal walls (Fig. 19.10) and cervical canal in postmenopausal women. In this population, it is frequent to find cervical stenosis (Fig. 19.11a–c) or synechiae

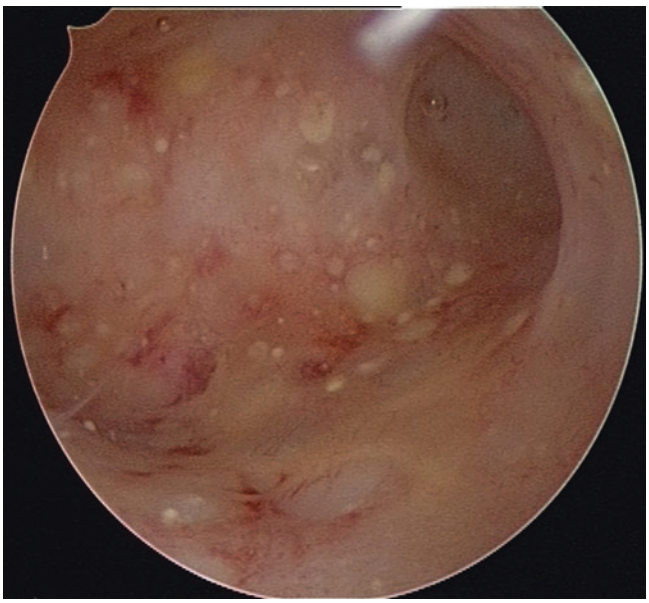

Fig. 19.9 Uterus with HRT

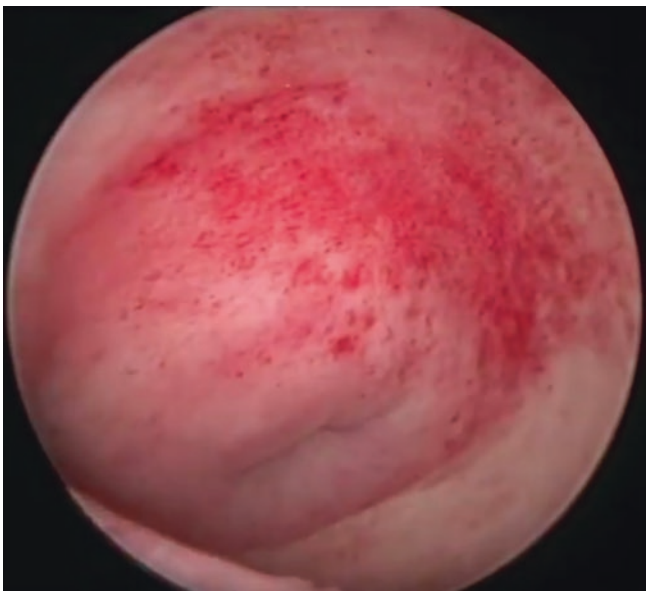

Fig. 19.10 Vaginal walls. Note the atrophy and pale color of the vaginal mucosa with some erythema due to atrophy

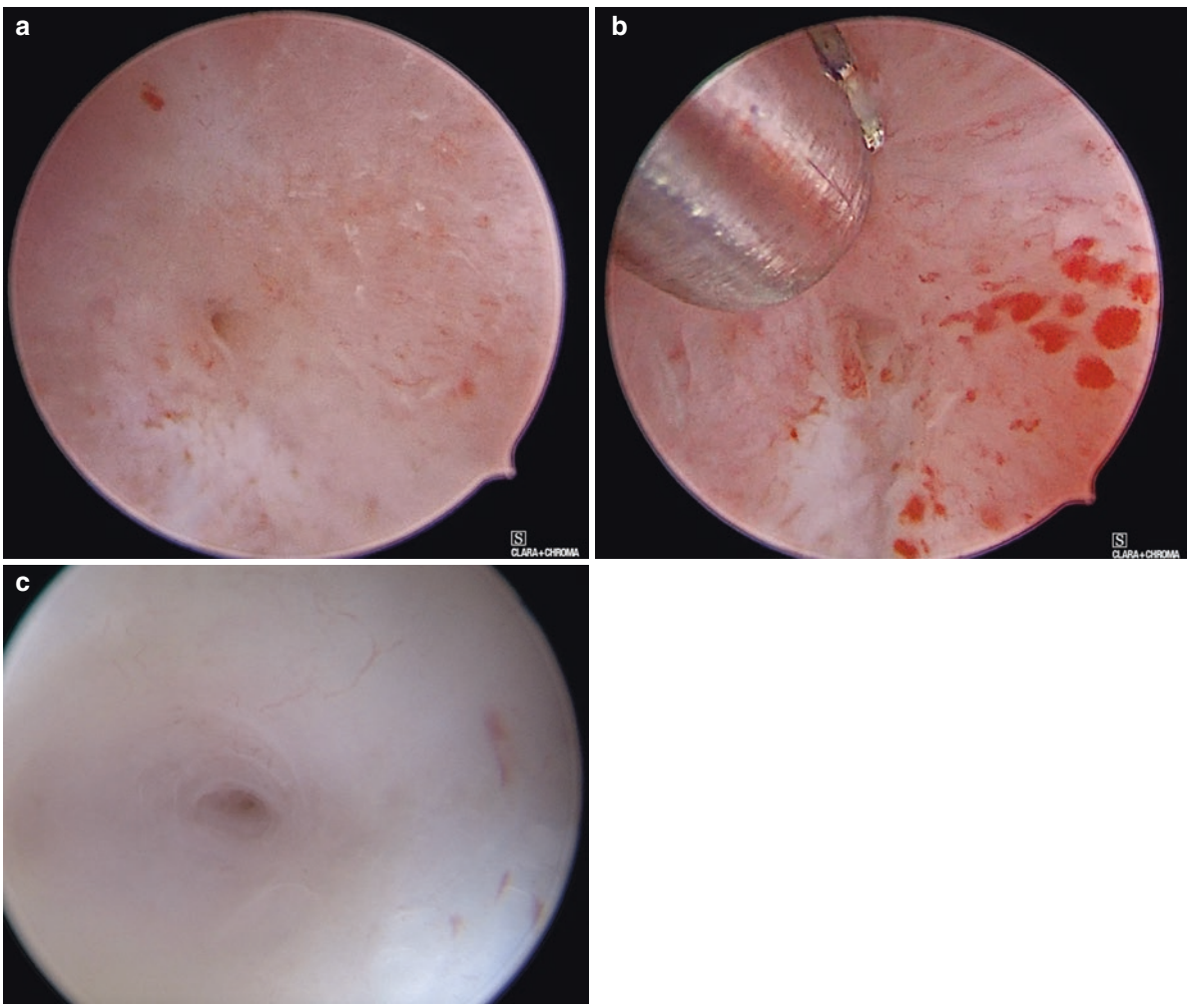

Fig. 19.11 (**a**) Stenotic external cervical os. Note the pinpoint size of the external cervical os. (**b**) Note the size of the external cervical os in comparison with the 5 French size hysteroscopic grasper. (**c**) Stenotic and scarred external cervical os in a postmenopausal patient with history of cold knife cone excisional procedure due to cervical dysplasia

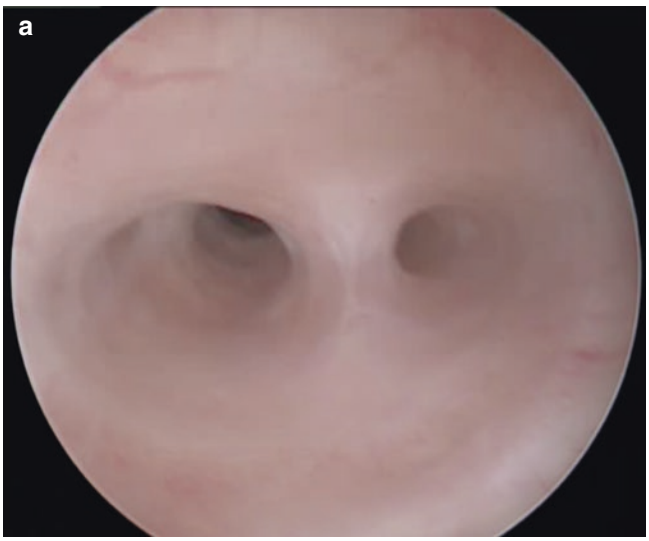

Fig. 19.12 Cervical synechia (**a**) Cervical synechiae in postmenopausal patient

(Fig. 19.12a, b) which are associated sometimes with the presence of mucus accumulation within the uterine cavity. In this scenario, recent evidence suggests that misoprostol does not have a significant effect on cervical ripening before hysteroscopy [22]. Another condition frequently encountered in clinical practice is the removal of foreign bodies (i.e., intrauterine device, IUD) from the uterine cavity that had been neglected over the years (Fig. 19.13). It is also important to note that in modern gynecology most of the intrauterine pathologies could be managed in an office setting, using hysteroscopes with a 5 Fr operating channel [23] or a 16 Fr mini-resectoscope [24].

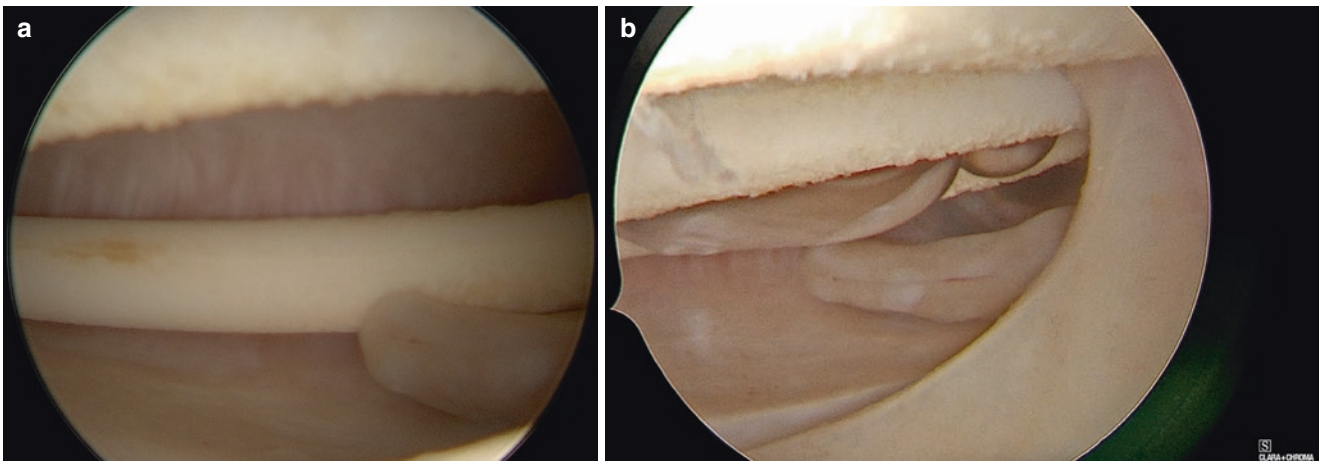

Fig. 19.13 Cervical synechiae. (**a**) Cervical synechiae in postmenopausal patient. (**b**) Cervical synechia video illustrating an in-office treatment of cervical synechia that allowed inspection of the uterine cavity

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Hysteroscopy During Pregnancy

20

José Alanis-Fuentes, Liliana Morales-Domínguez, and Abril Camacho-Cervantes

20.1 Introduction

The hysteroscopy during gestation from its beginnings focused on the endoscopic exploration of the embryo or the fetus regarding the evolution of its development having extra-amniotic observations by transcervical approach, which some authors denominate embryofetoscopy. In some cases where a biopsy of embryonic tissue to avoid contamination with maternal and placental tissue is required, hysteroscopy is used. The first reports of Björn in 1954 were made in patients prior to therapeutic abortions during the first and second trimesters. The study of Agüero in 1966 was performed at various moments of pregnancy—including transparto, and with indications that at the time were valid in the absence of ultrasound. While in the 1970s hysteroscopy was used as a prenatal diagnostic technique being displaced by ultrasound, with the miniaturization of the instruments in the 1990s the technique of embryoscopy with directed biopsy was surpassing the interventional ultrasound techniques when diagnosing several syndromes that were not detectable by DNA analysis [1].

Indications in arrested gestations diagnosed by vaginal ultrasound with gestational age <10 weeks (embryonic period) or 11–12 weeks (beginning of fetal period) by any of the following criteria of Filly in 1994 were as follows: (1) clear visualization of an amniotic sac without an embryo; (2) absence of an embryonic heartbeat of CRL >5 mm; (3) absence of embryo in gestational sac of medium diameter >18 mm; (4) absence of a vitelline vesicle in a gestational sac with a mean diameter >13 mm.

The removal of the intrauterine device (IUD) in early pregnancy became relevant, given the potential complications of its permanence during pregnancy as reported by Howard J. Tatum et al. in 1976. Striking was the limitation in the first trimester, attributing potential injury to the optic nerve of the fetus, which is considered erroneous, as we demonstrated in our study [2].

In 1998 Carrera wrote about the limitations of hysteroscopy during pregnancy. His report was limited to the extraction of IUD during the first trimester of pregnancy, also attributing probable optic nerve injury or rupture of the gestational sac, taking as reference the Spanish Association of Hysteroscopy (Photos 20.1, 20.2, and 20.3).

In 2014 during the sessions of the IX Congress of the Gynecological Endoscopy Section of SEGO and 10th AAGL International Congress on Minimally Invasive Gynecological Surgery in Barcelona, Spain, we presented the first surgical

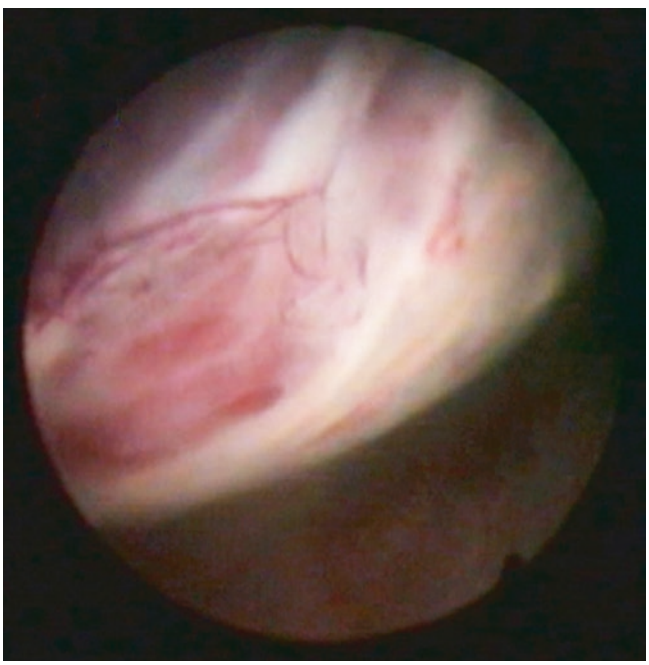

Photo 20.1 Appearance of a gestational sac

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_20) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_20

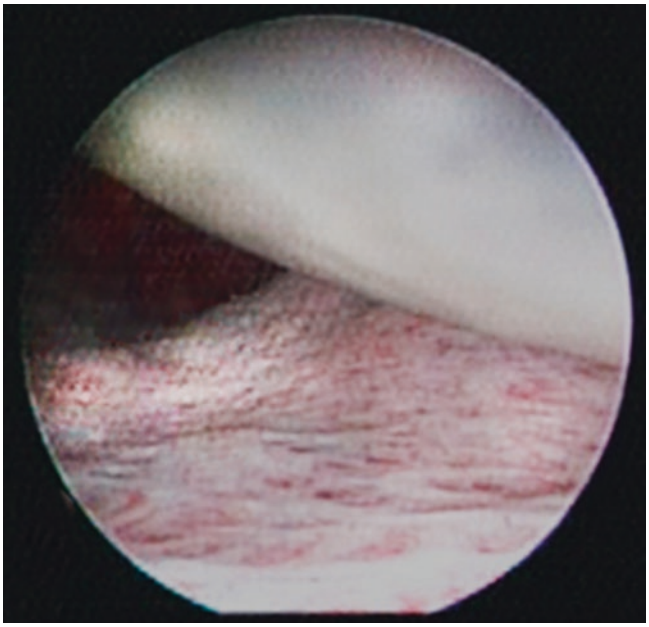


Photo 20.2 Crateriform endometrium characteristic of pregnancy

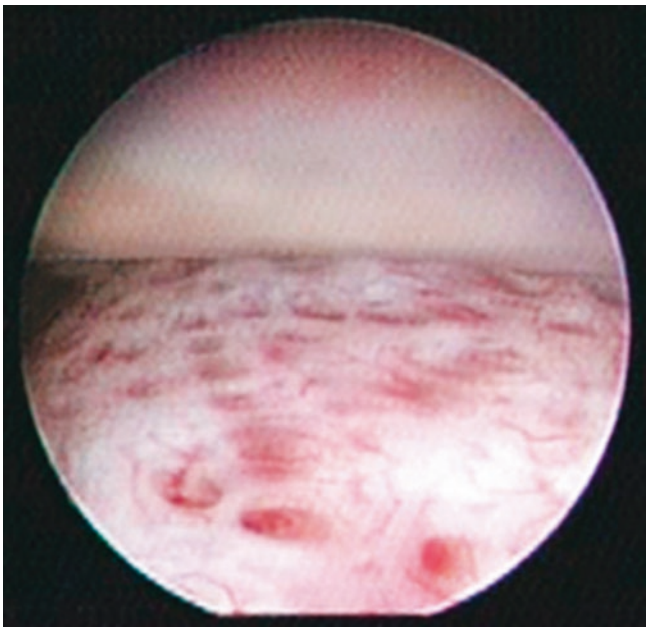


Photo 20.3 Detail of the features of the crateriform endometrium during pregnancy

hysteroscopy in a pregnant woman which consisted of the removal of a polyp located at isthmus and was protruding outside the external cervical os. We also showed the initial work of visual acuity in children whose mothers had their IUD removed during their pregnancy [2].

Hysteroscopic surgery has evolved according to technological development. From the birth of hysteroscopic access by vaginoscopy, the principle of see and treat, the knowledge of uterine anatomy, and the incorporation of bipolar energy applied to the hysteroscope as well as the diode laser, nowadays a large number of procedures can be performed in the office and without anesthesia [3–13].

Our indications in 2018 are listed in Table 20.1.

Table 20.1 Hysteroscopy in pregnancy indications

Hysteroscopy in pregnancy indications 2018
Related conditions to pregnancy
Polyp of the implantation site
Retained products of the conception
Placental cretism
During pregnancy
Embryoscopy
Fetoscopy
Embryonic reduction
Chorionic villus sampling
Removal of foreign bodies
Metroplasty during pregnancy
Endocervical polyps
Ectopic pregnancy
Cervical pregnancy
Heterotopic pregnancy
Cornual pregnancy

20.1.1 Polyp at the Implantation Site

Placental site trophoblastic tumor is the second rarest tumor of the trophoblastic disease, with less than 300 cases reported. Clinical presentation is a diagnostic challenge; it has an unpredictable malignant potential, and it can develop in choriocarcinoma or even have a simultaneous presentation. The prevalence reported is of 1/1,000,000. Several aspects of the surgical procedure are shown until its complete resection (Photos 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, 20.10, and 20.11).

20.1.2 Retained Products of Conception and Placental Accretism

In women with medical abortion of a first-trimester pregnancy who use the mifepristone/misoprostol protocol with incomplete expulsion of pregnancy, a uterine evacuation may be indicated. This procedure can be performed with dilatation and curettage or with operative hysteroscopy. In these cases, hysteroscopy as a treatment of retained products of conception followed by either childbirth or different types of abortion can be used—a topic that will be discussed in a separate chapter (Photos 20.12, 20.13, 20.14, 20.15, 20.16, 20.17, 20.18, and 20.19).

20.1.3 Placental Accretism

Defined as placental accretism, it is the abnormal partial or total adherence of the placenta to the underlying uterine surface (Photos 20.20, 20.21, 20.22, and 20.23).

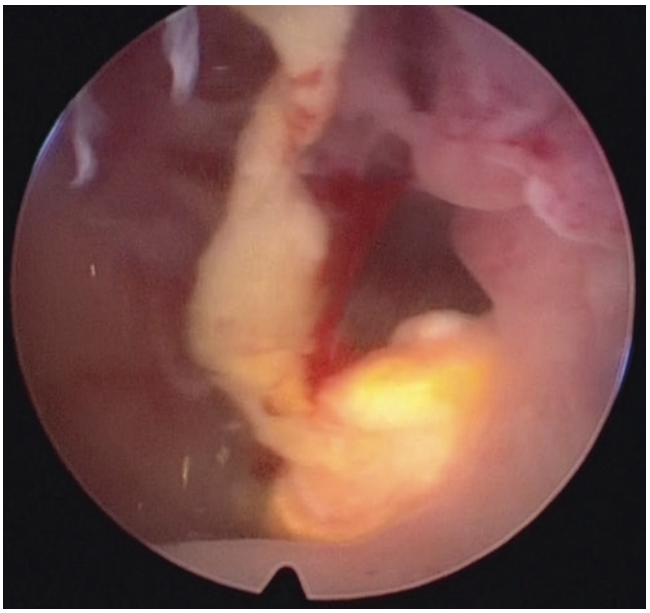


Photo 20.4 Panoramic view of a polyp at the implantation site

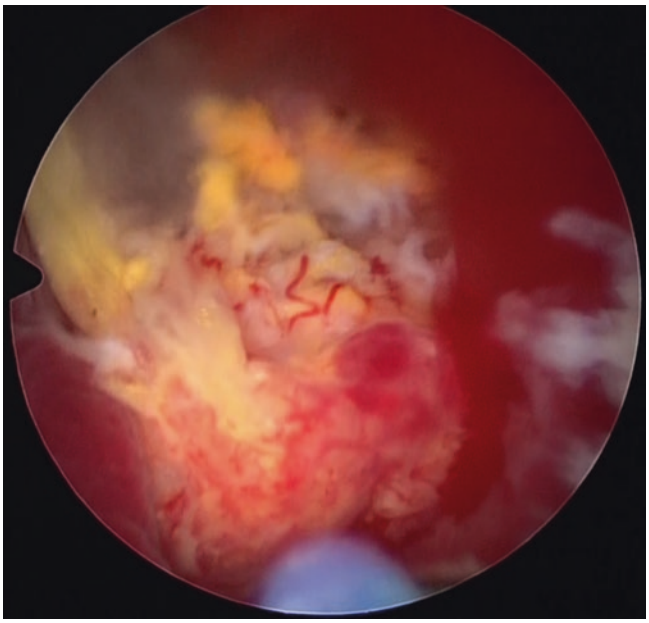


Photo 20.6 Top view of the polyp that shows the vascularity

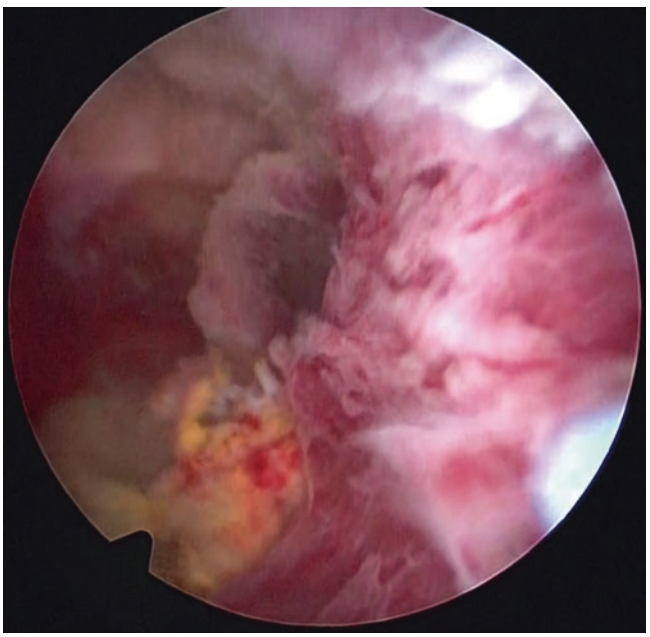


Photo 20.5 Location detail

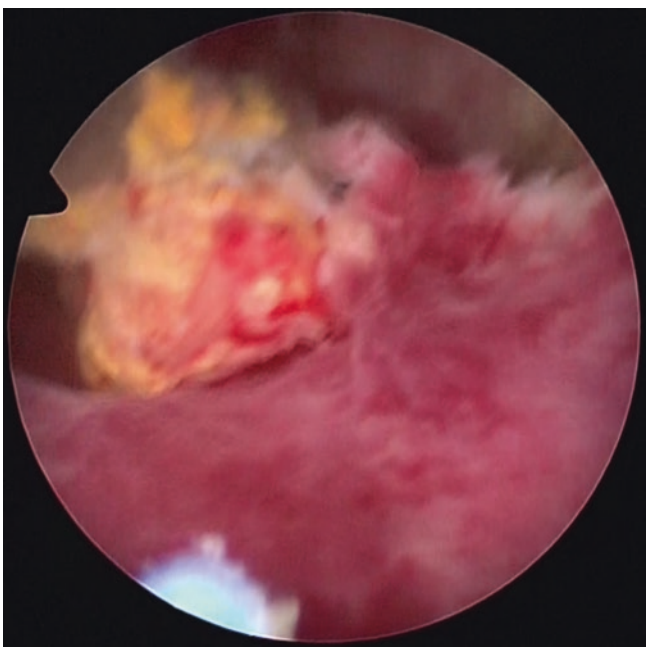


Photo 20.7 Detail of the vascularity at the base of the polyp

20.2 During Pregnancy

20.2.1 Embryoscopy and Fetoscopy

Embryo's biopsies taken by hysteroscopy are already a fact and they are carried out in 97% of the cases successfully, thus achieving the differentiation between embryonic material. The biopsy of the mother within the study of anembryonic pregnancy is another subject that can be investigated because sometimes embryonic tissue could be found, showing a necrosis of the cord secondary to thrombophilia. Prof. Phillip et al. will show his work in a separate chapter (see Video 20.1) (Photos 20.24, 20.25, 20.26, 20.27, and 20.28).

20.2.2 Fetoscopy

By the year 2000, Greco and collaborators proposed the hysteroscopy of the embryo and fetuses as a method of study and research before the surgical interruption of pregnancy (Photos 20.29, 20.30, 20.31, 20.32, 20.33, 20.34, and 20.35).

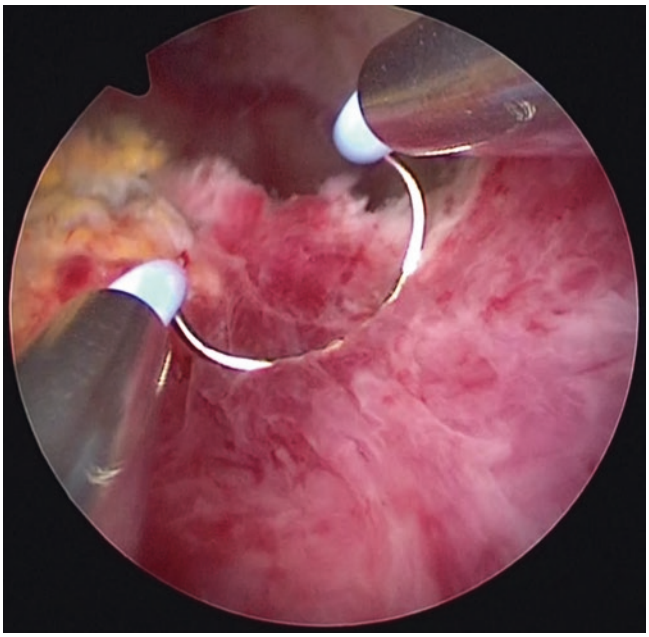


Photo 20.8 Palpating the polyp's anatomical limit

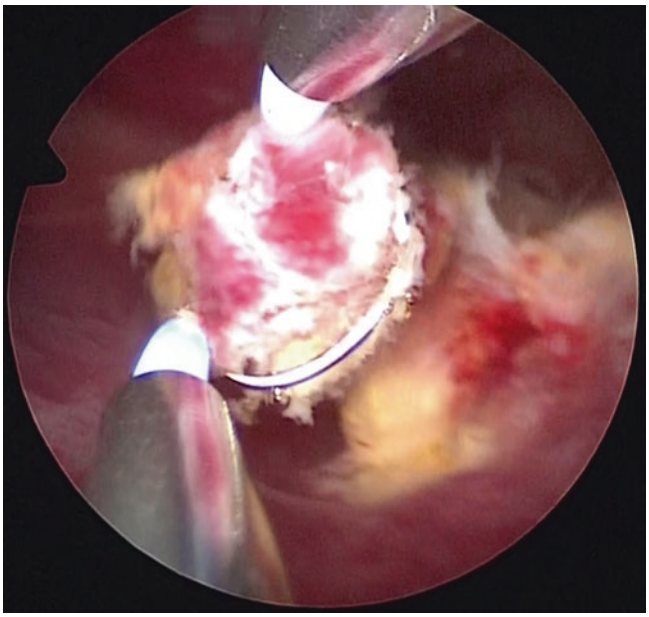


Photo 20.10 The cut of the polyp base is done using a resector with bipolar coagulation

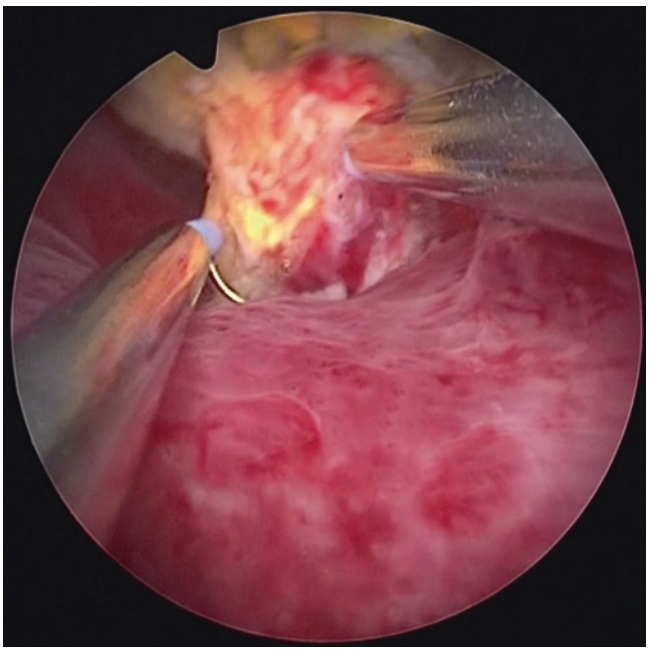


Photo 20.9 Feeling the consistency of the base with the loop

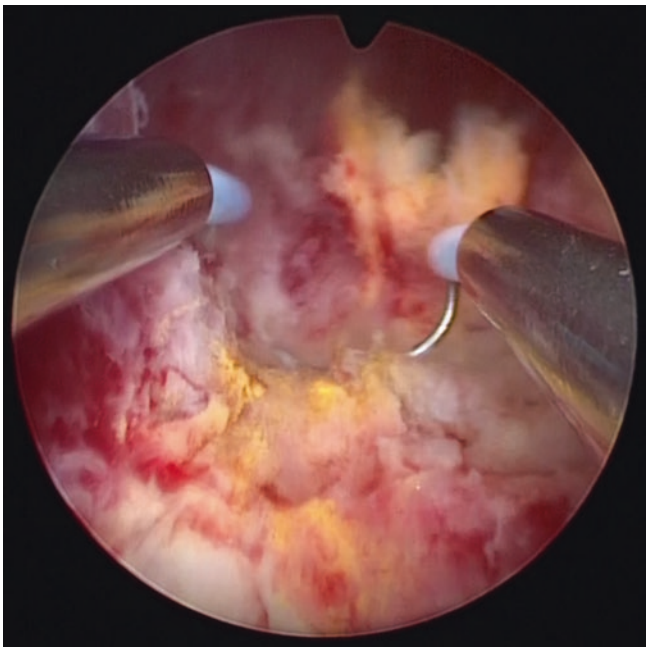


Photo 20.11 Final view after the complete excision of the polyp with bipolar energy

20.2.3 Embryonic Reduction

Embryonic reduction, although prohibited in many countries, is also a reality for hysteroscopy. There are selection criteria to decide on the future of embryos and sufficient evidence regarding the reduction of complications such as preterm delivery and preeclampsia in multiple pregnancies (Photos 20.36, 20.37, 20.38, and 20.39).

20.3 Chorionic Villus Sampling

20.3.1 Chorionic Villus Sampling

Chorionic villus sampling (CVS) is a prenatal test that involves taking a sample of tissue from the placenta to test for chromosomal. By taking a biopsy under direct vision by

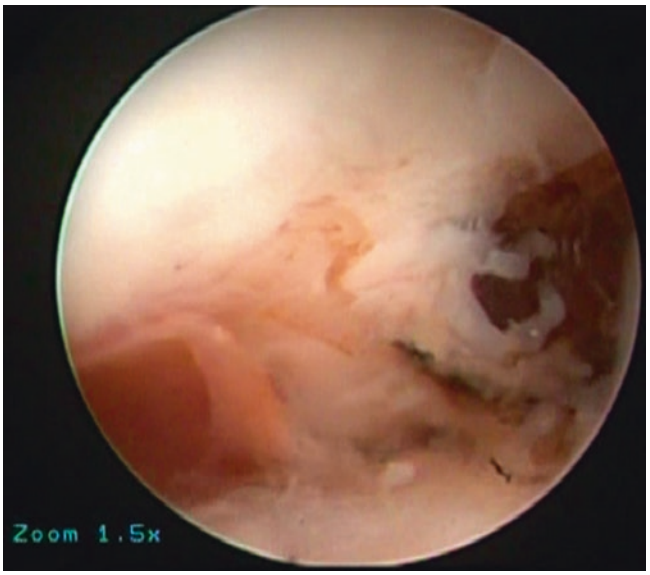


Photo 20.12 Panoramic view of chorionic villi

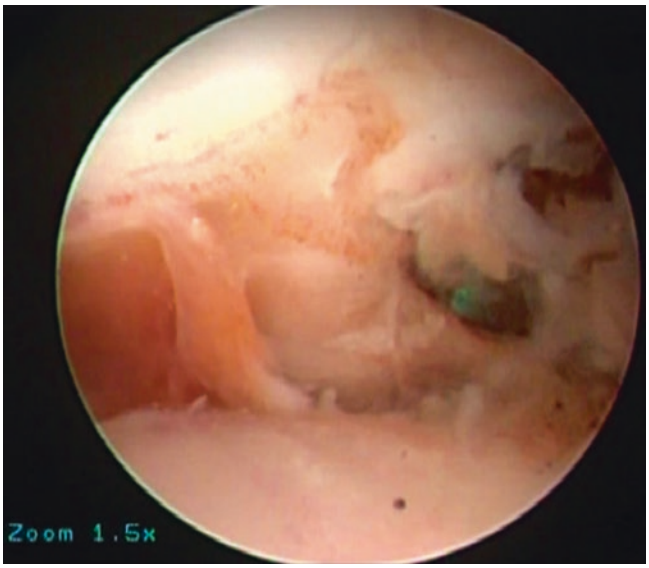


Photo 20.14 View of the lesion after the laser cut

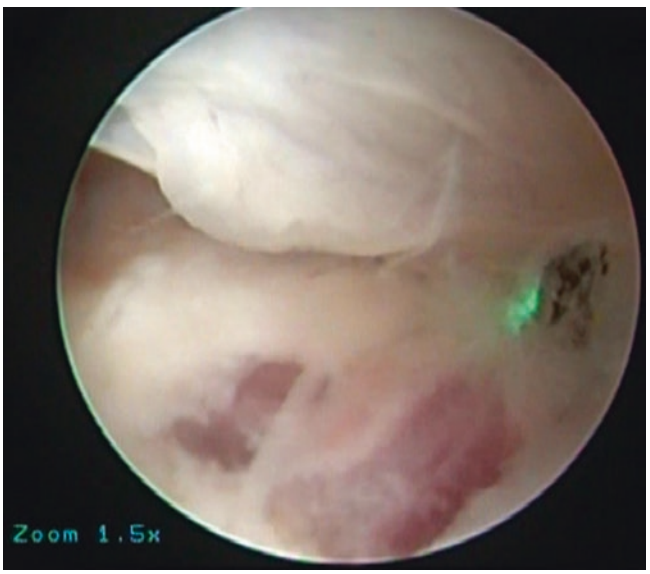


Photo 20.13 Effect of laser energy on tissue

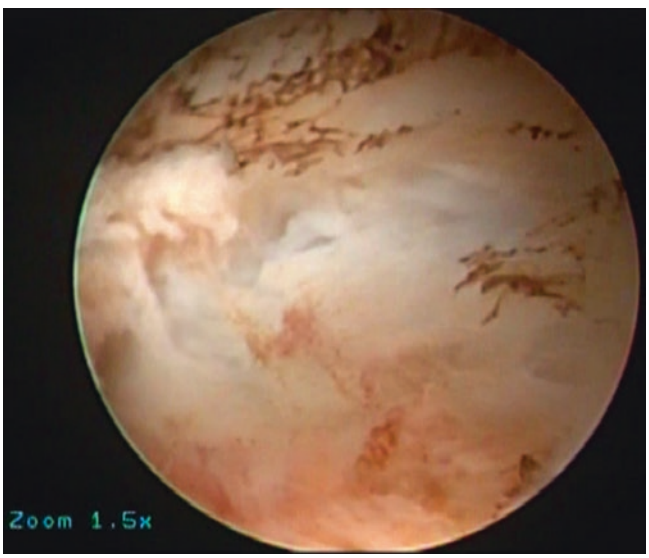


Photo 20.15 View of vascularity coagulated with laser

hysteroscopy, contamination of the sample with maternal tissue is reduced, allowing more precise diagnoses (Photos 20.40, 20.41, 20.42, 20.43, 20.44, and 20.45).

20.3.2 Removal of Foreign Bodies

Since its inception, hysteroscopy during pregnancy was prescribed only for the removal of IUD during the first trimester, and later for also being carried out during the second trimester of the gestation since with modern equipment practically there are no losses of the pregnancy (see Video 20.2).

20.3.3 Metroplasty During Pregnancy

Partial uterine septal metroplasty has only been reported in one case worldwide in a pregnant woman with a history of multiple abortions. The procedure was performed in Mexico and was done under patient request, achieving a full-term pregnancy with the birth of a female product. The case was shown in the IX Congress of the Gynecological Endoscopy Section of SEGO and 10th AAGL International Congress on Minimally Invasive Gynecological Surgery in Barcelona, Spain (Photos 20.46, 20.47, 20.48, 20.49, and 20.50).

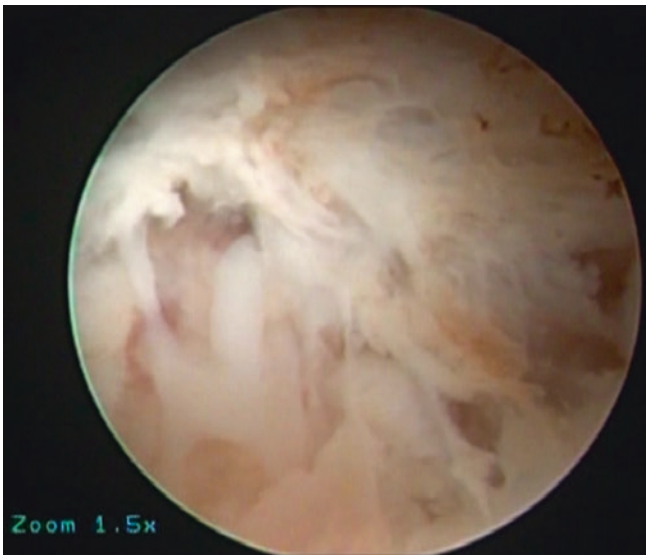


Photo 20.16 Detail of the chorionic villi

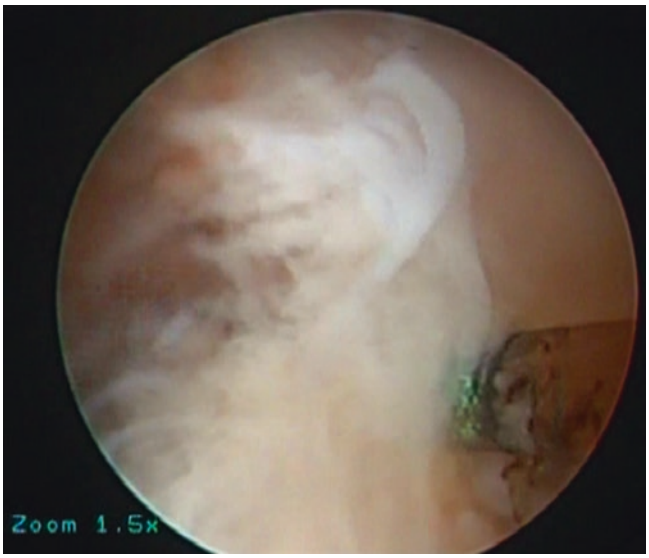


Photo 20.18 Laser section of chorionic villi

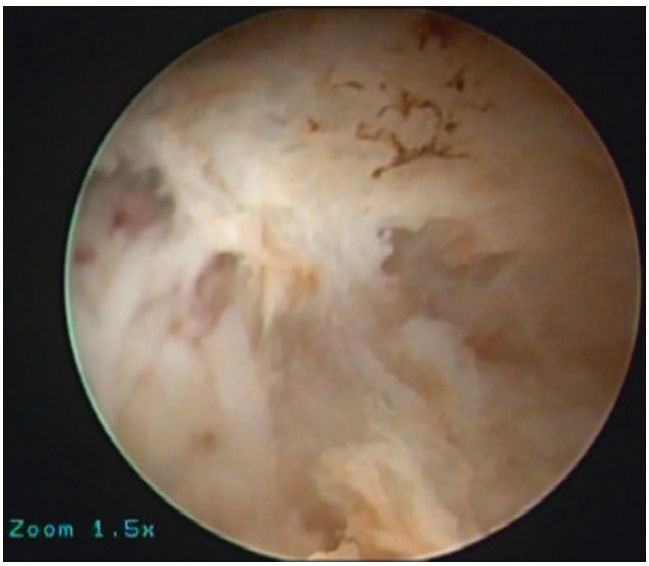


Photo 20.17 View of the separation between the chorionic villi and the uterine wall

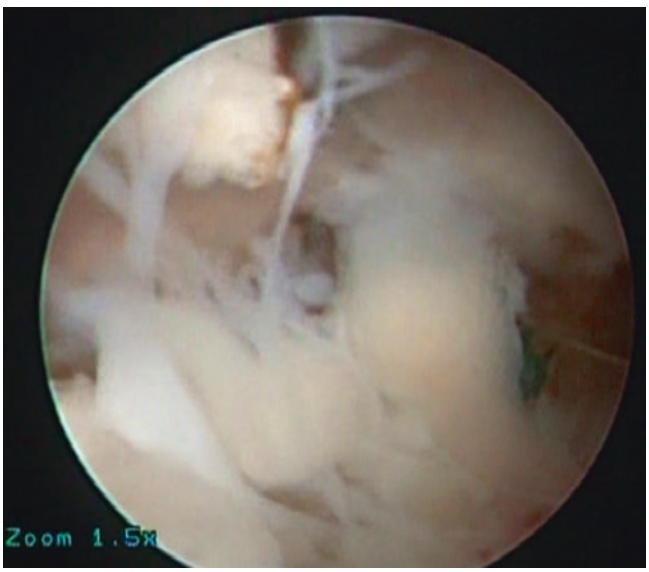


Photo 20.19 Detail of the laser cut

20.3.4 Cervical Pathology (Polyps)

The endocervical polyp can affect up to 10% of women and may appear during pregnancy. The therapeutic approach depends on the size of the polyp and the discomfort it is causing. If it is a polyp that causes cervical dilation, we remove it under hysteroscopic vision; otherwise we only observe it and in case of persistence after delivery or C-section we also remove it by hysteroscopy (Photos 20.51, 20.52, 20.53, 20.54, 20.55, and 20.56).

20.4 Ectopic Pregnancy

20.4.1 Cervical Pregnancy

Cervical ectopic pregnancy is an exceptional entity, which affects fertility, and is associated with high morbidity and mortality, and remains as a life-threatening condition. It has been described to have a mortality rate as high as 50% in patients with diagnosis of cervical ectopic pregnancy who were treated with hysterectomy. Improved ultrasound resolution and earlier detection of these preg-

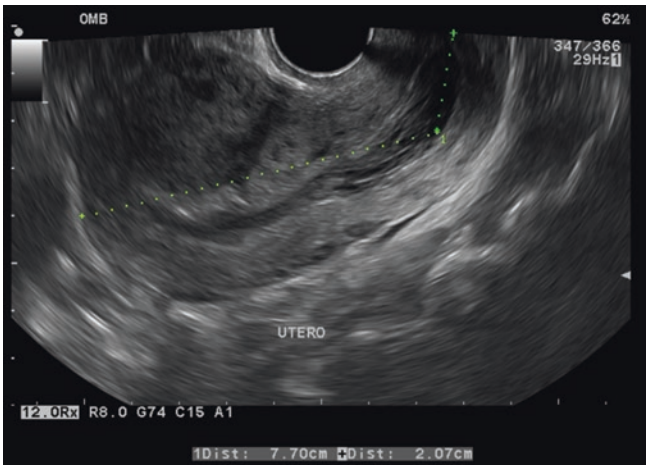


Photo 20.20 Ultrasound view of the tumor

nancies have led to the development of more conservative treatments. Cervical ectopic pregnancy represents a challenge, since an early diagnosis and treatment are critical to avoid serious complications such as severe hemorrhage and need for hysterectomy. Even today, the most effective method of its management is under investigation, and should be individualized according to the clinical presentation. When medical management with systemic methotrexate fails, or in the presence of fetal cardiac activity, we have performed hysteroscopic resection with either bipolar needle, bipolar loops, or diode laser with satisfactory results (see Video 20.3) (Photos 20.57, 20.58, and 20.59).

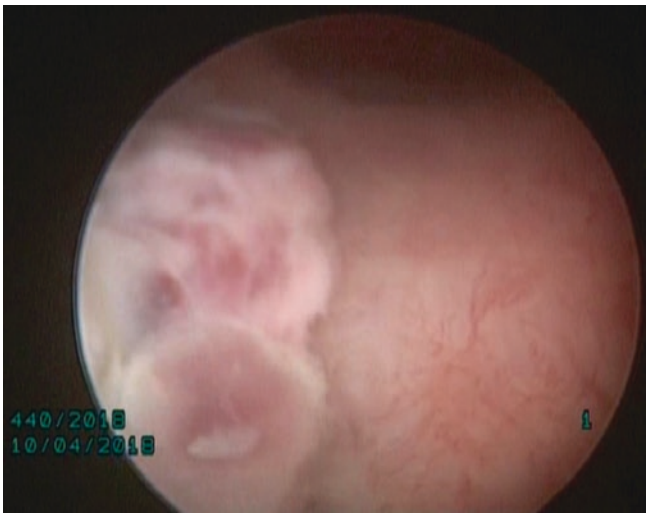
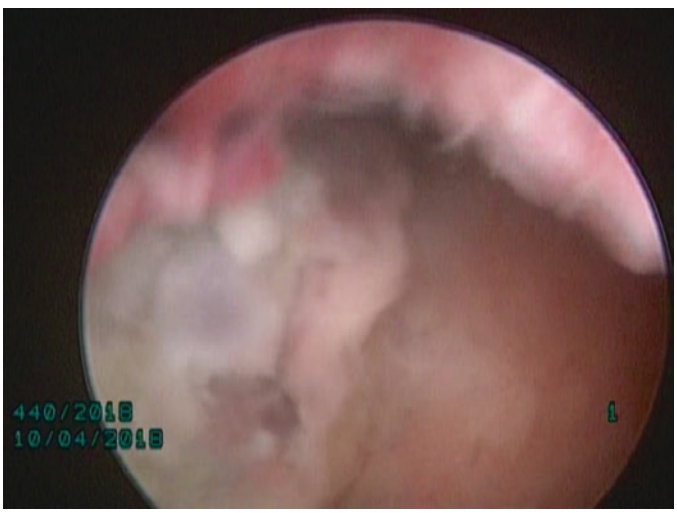
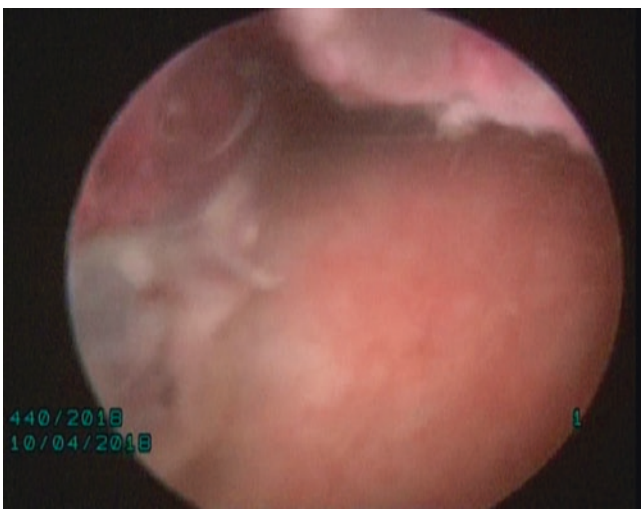


Photo 20.21 Hysteroscopic view of the lesion

Photo 20.24 Pregnancy of 15 days of gestation





Photos 20.22, 20.23 Detail of the appearance of the tumor

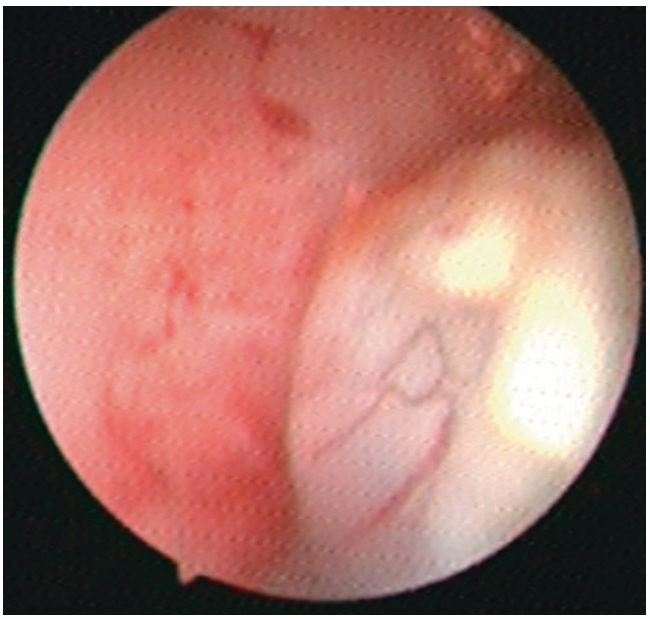


Photo 20.25 Detail of the gestational sac

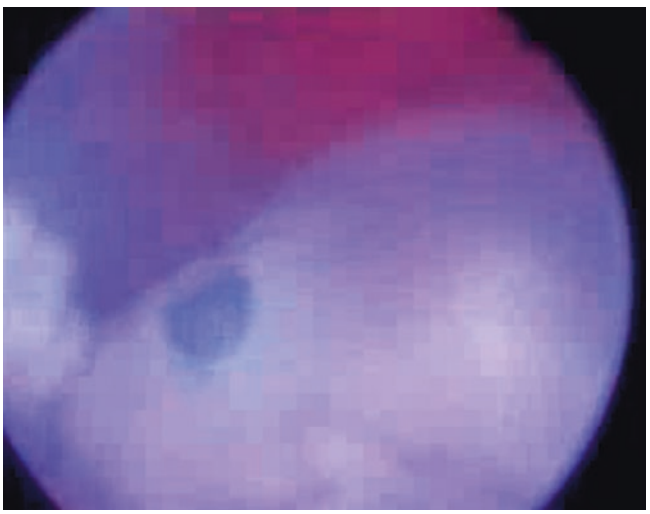


Photo 20.26 View of the face and hand

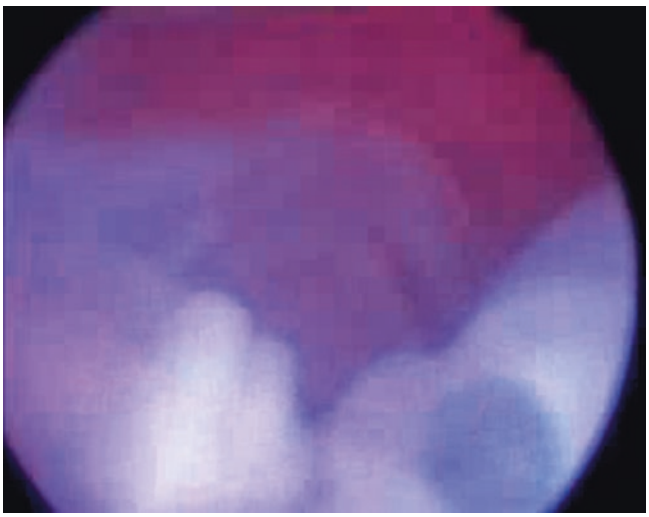


Photo 20.27 Detail of the umbilical cord

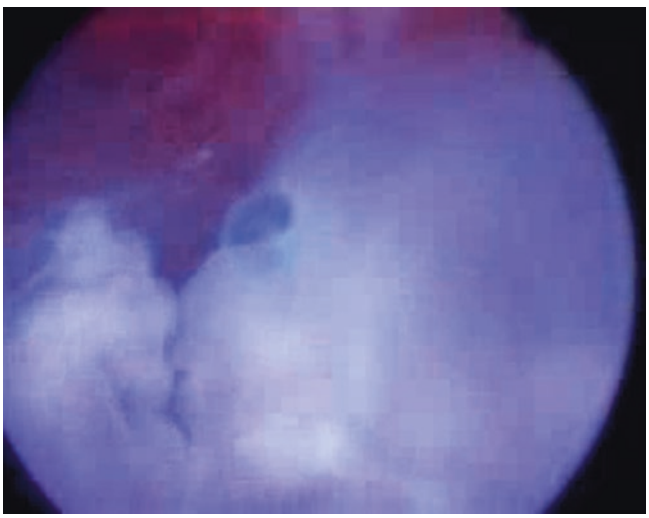


Photo 20.28 View of the hand and mouth

20.4.2 Cornual Pregnancy

Cornual (interstitial) ectopic pregnancy is an uncommon variant of ectopic pregnancy, with an incidence of 1.5% of all ectopic pregnancies. It represents a diagnostic and therapeutic challenge with a significant risk of rupturing and bleeding. Thus, an early diagnosis is essential. Usually the first line of treatment consists of systemic methotrexate therapy, which in advanced interstitial pregnancies is generally ineffective. Prior to rupture, the cornual ectopic can be managed by laparoscopy. We present the case of a cornual ectopic pregnancy, with fetal cardiac activity, where systemic methotrexate was ineffective. We performed an operative hysteroscopic, with the complete resection of the cornual ectopic pregnancy. In the graphic sequence several steps of the procedure are shown (see Videos 20.4, 20.5, and 20.6).

20.4.3 Cervical Pregnancy in Isthmocele

Cesarean scar pregnancy is a rare form of ectopic pregnancy; the management of the cervical pregnancy in the isthmocele represents a challenge. The major risk of this type of pregnancy is the early uterine rupture; thus, active management of these pregnancies starting immediately after diagnosis is crucial. Therapeutic options can be medical, surgical, or a combination; the local inflamed tissue at the isthmocele dome should be removed by laparoscopy, combined laparoscopic-vaginal or vaginal surgery, and operative hysteroscopy. Hysteroscopy or laparoscopic

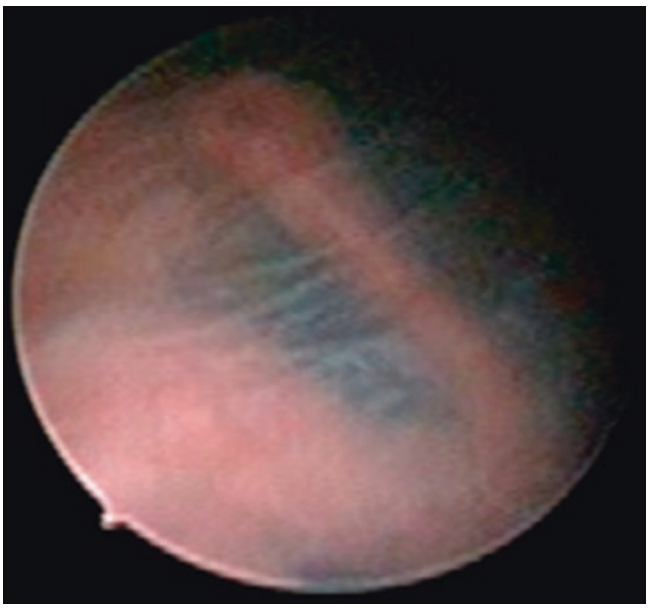


Photo 20.29 Complete view of the arm, hand, and part of the skull

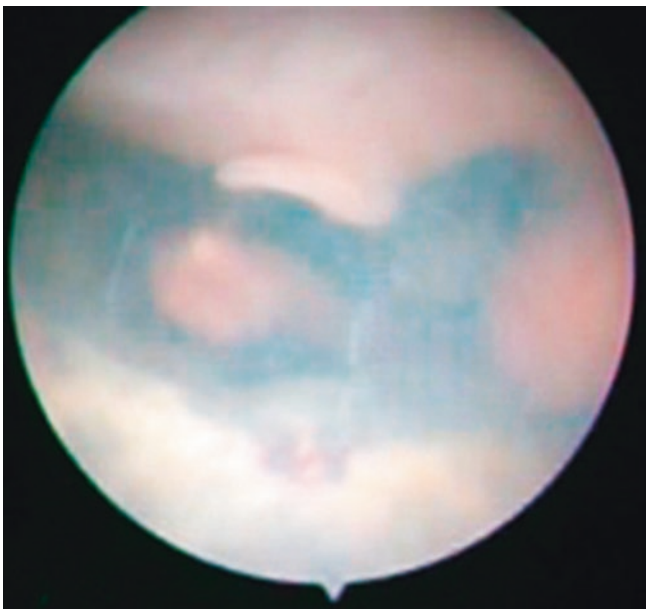


Photo 20.31 Detail of the ear and hand

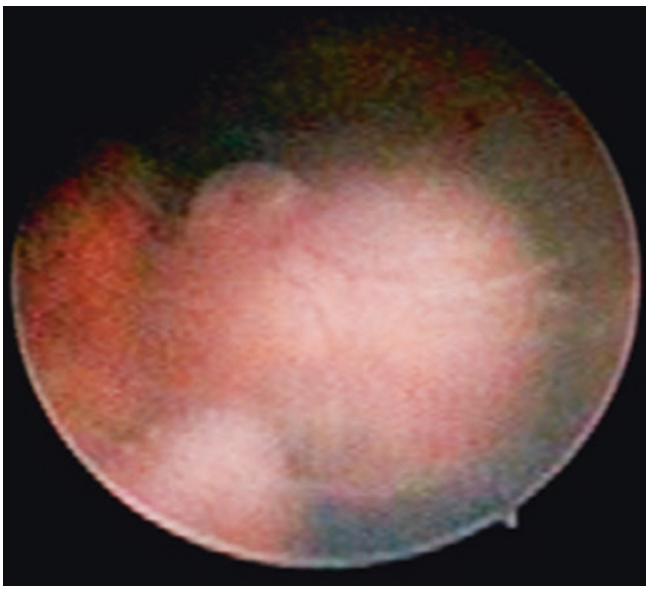


Photo 20.30 View of the face of the fetus

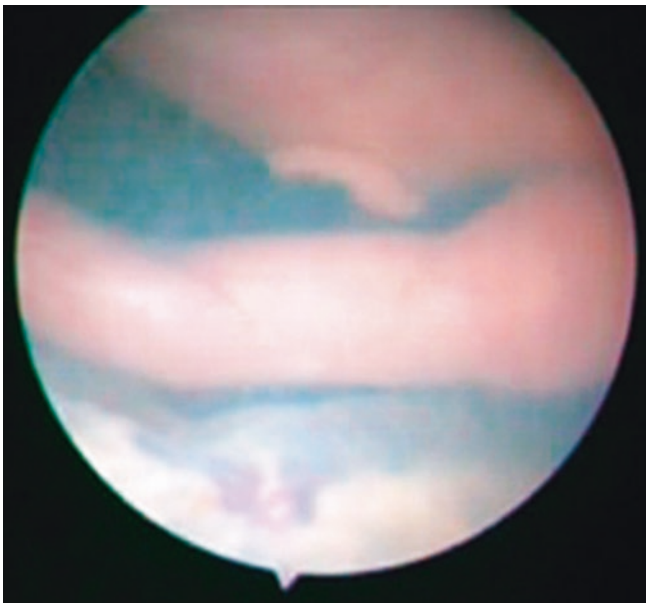


Photo 20.32 View of the arm

hysterotomy seems to be the best first-line approach to treating cesarean scar ectopic pregnancy (see Video 20.7).

20.4.4 Heterotopic Pregnancy (Cervical and In Situ)

The incidence of heterotopic pregnancy is very low; the frequency is estimated to be 1 in 30,000 pregnancies. However, more recent data indicate that the rate is higher due to assisted reproduction and is approximately 1 in 7000 overall, and as high as 1 in 900 with ovulation induction. We present a rare case of heterotopic pregnancy with live intrauterine gestation and cervical ectopic pregnancy. This represents a challenge in the resolution of the ectopic pregnancy, since the intrauterine live gestation should be allowed to continue.

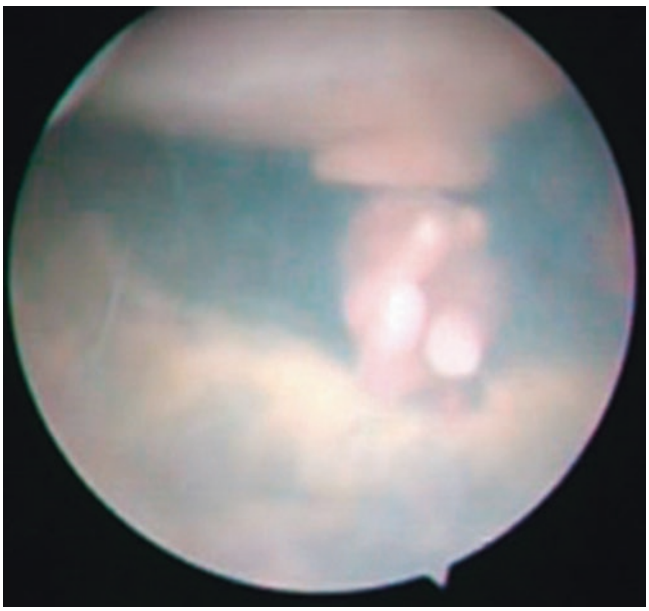


Photo 20.33 Detail of the fingers

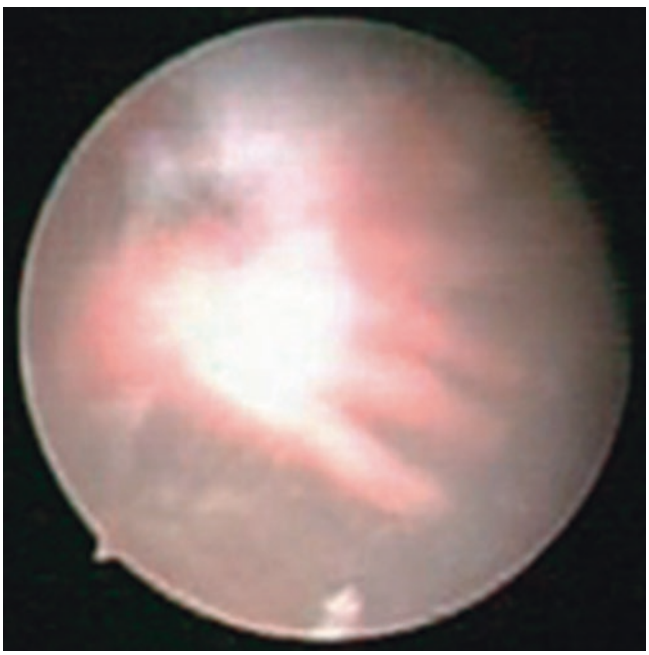


Photo 20.34 Detail of the hands

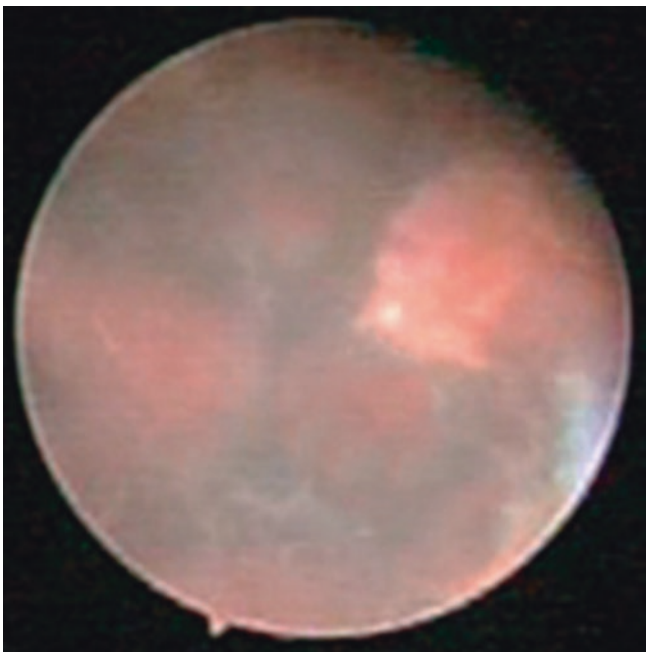


Photo 20.35 Detail of the feet

Photo 20.36 Perforation of the gestational sac

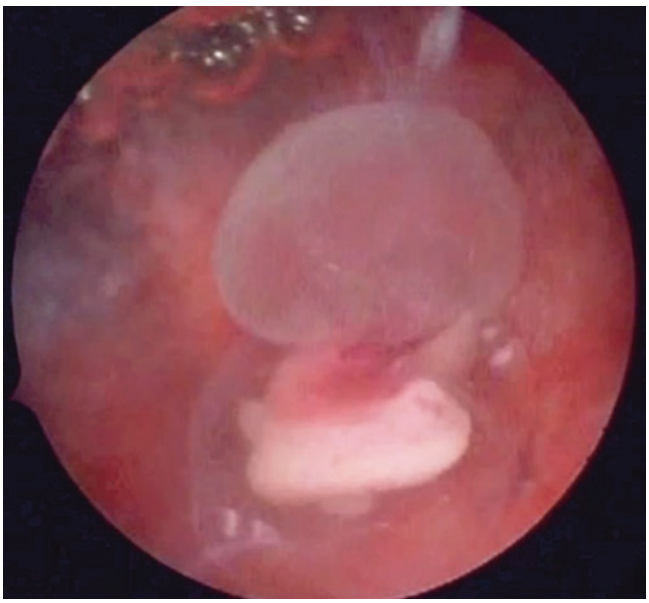


Photo 20.37 Panoramic view of the 5-week embryo

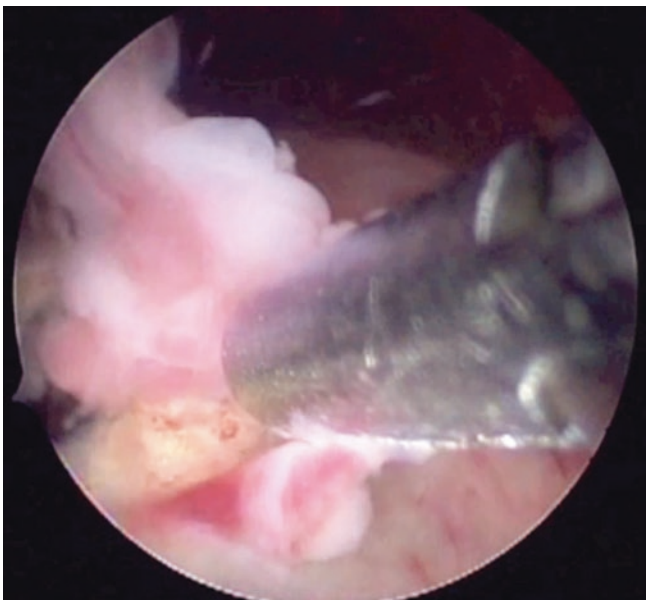


Photo 20.39 Section and traction of the umbilical cord

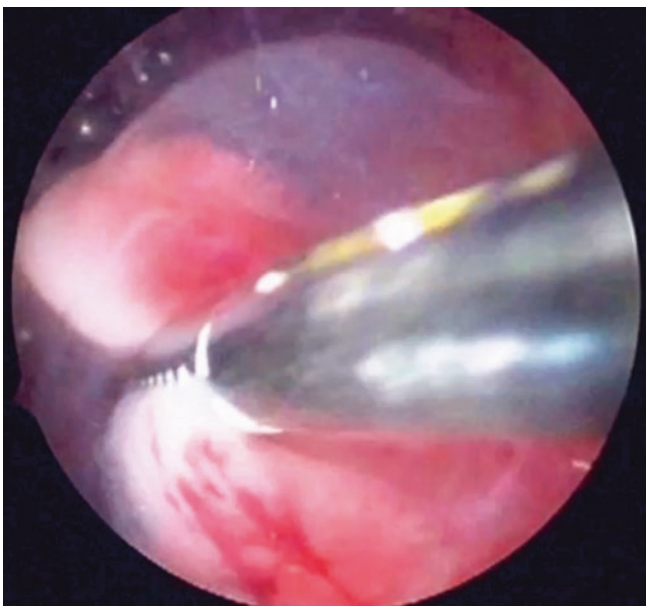


Photo 20.38 Clamping the umbilical cord

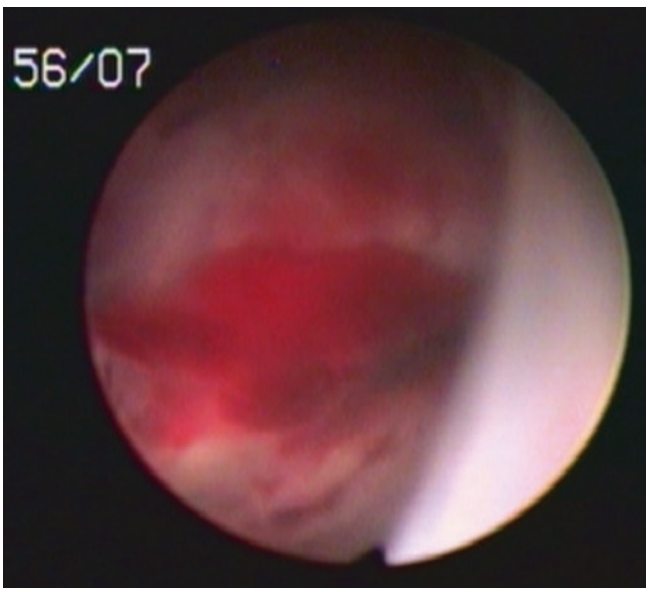


Photo 20.40 View of the gestational sac

Photo 20.41 Detail of the gestational sac

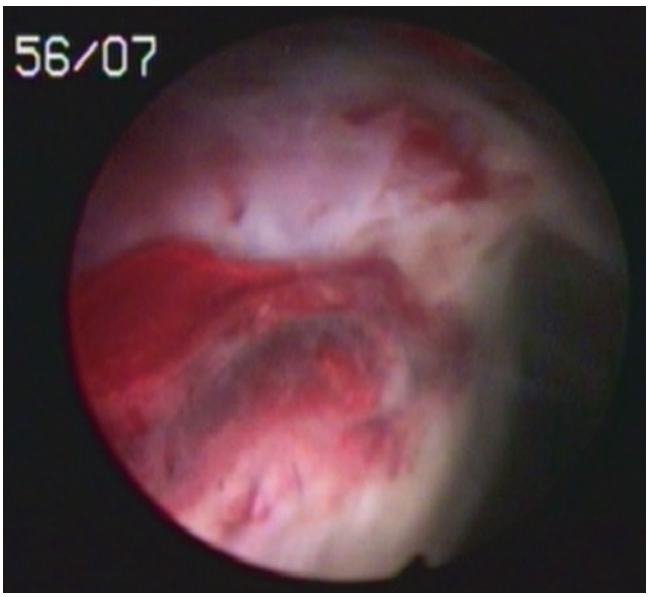


Photo 20.43 Close-up to the implantation site

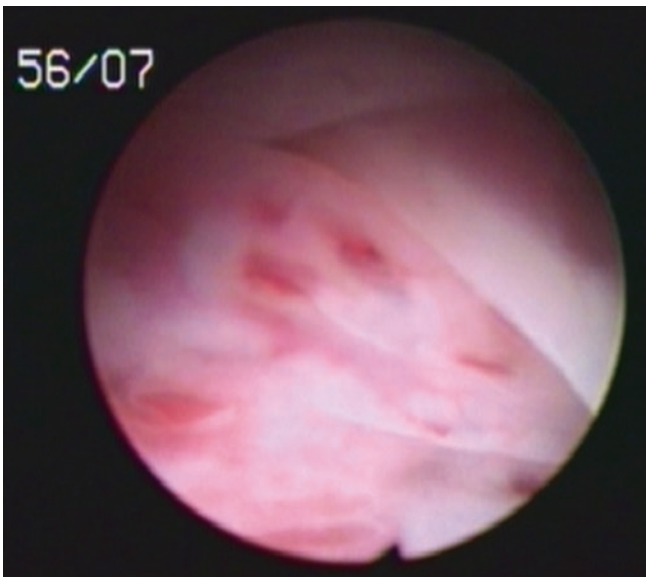


Photo 20.42 Selection of the biopsy site

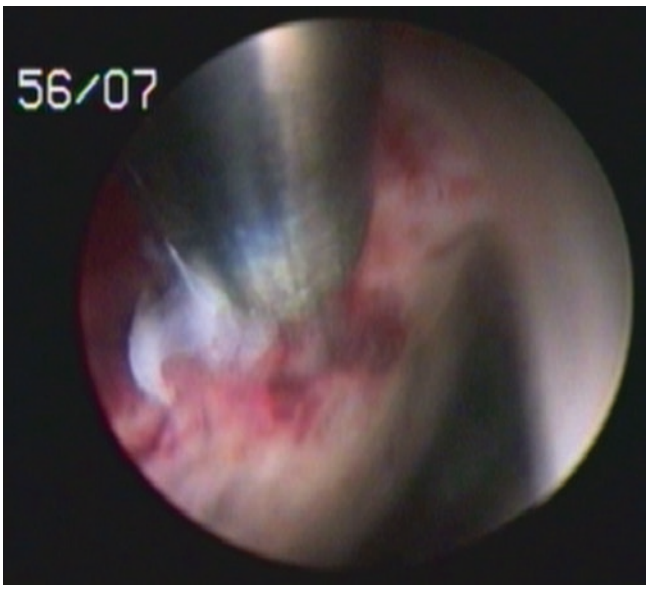


Photo 20.44 Taking the biopsy

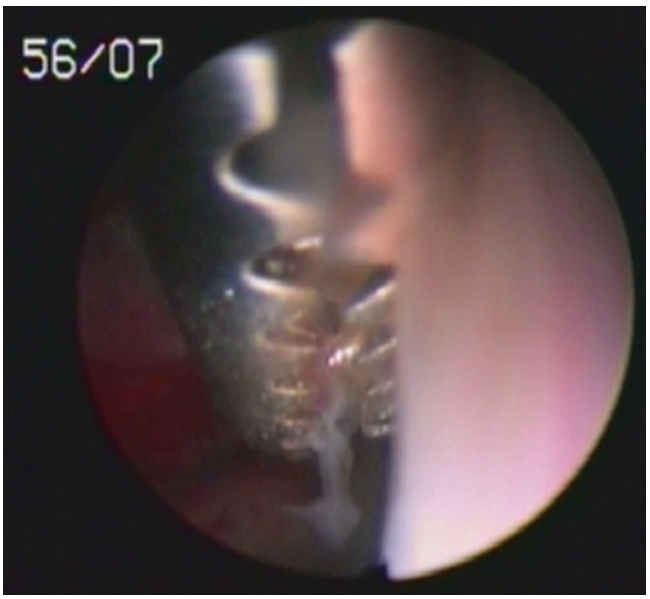


Photo 20.45 Detail of the biopsy taken inside the grasper

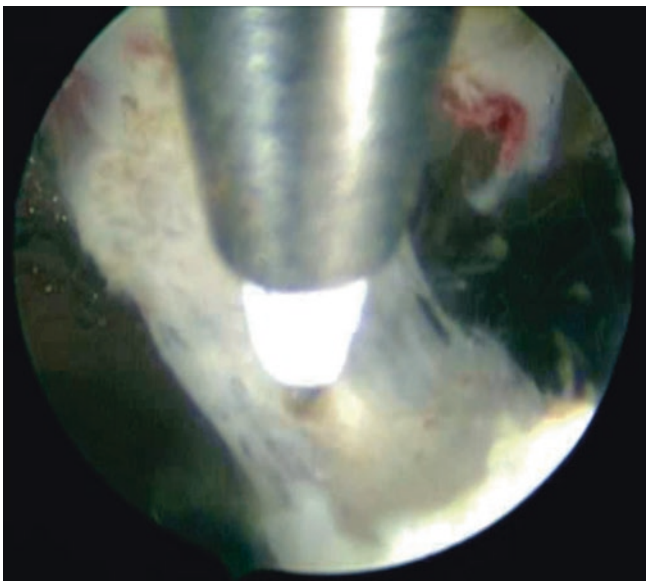


Photo 20.47 Detail of the cut of the septum with bipolar electrode

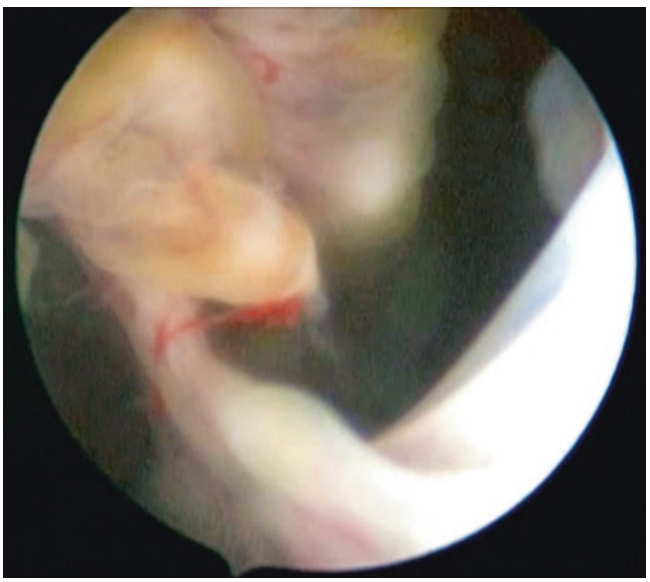


Photo 20.46 View of partial uterine septum

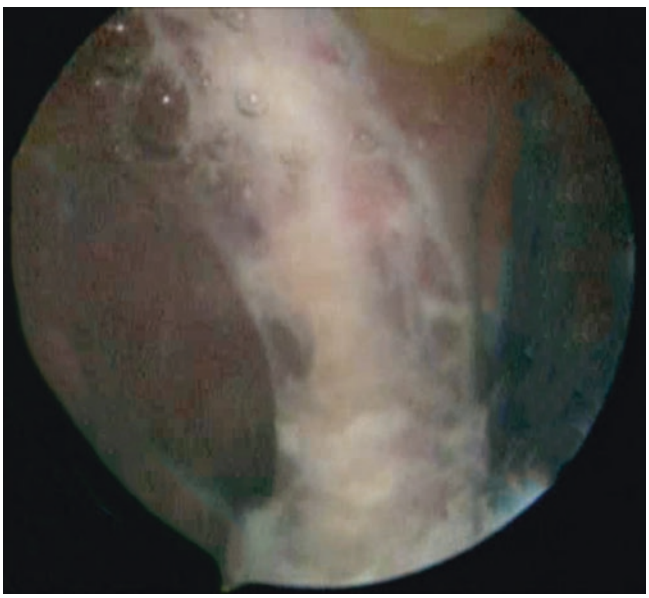


Photo 20.48 View of the septum cut

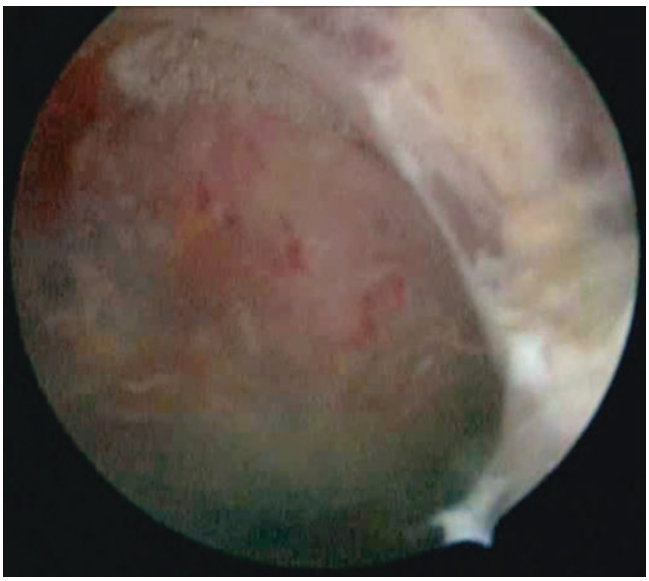


Photo 20.49 The gestational sac is seen on the left side of the photograph in close relation to the uterine septum

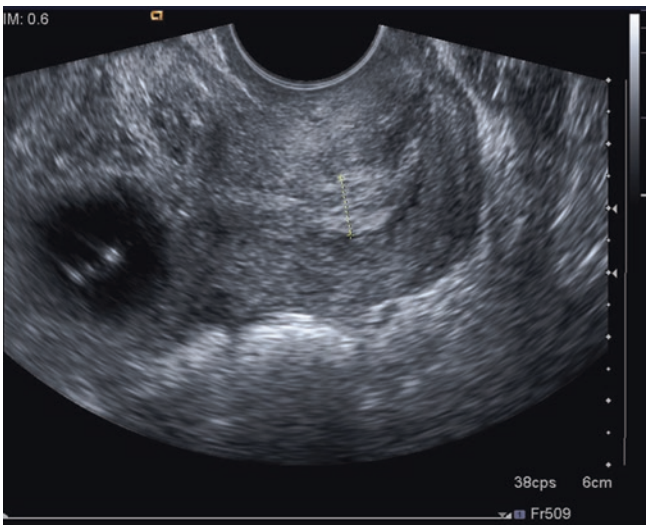


Photo 20.51 Ultrasound view of the location of the pregnancy with respect to the cervical location of the polyp

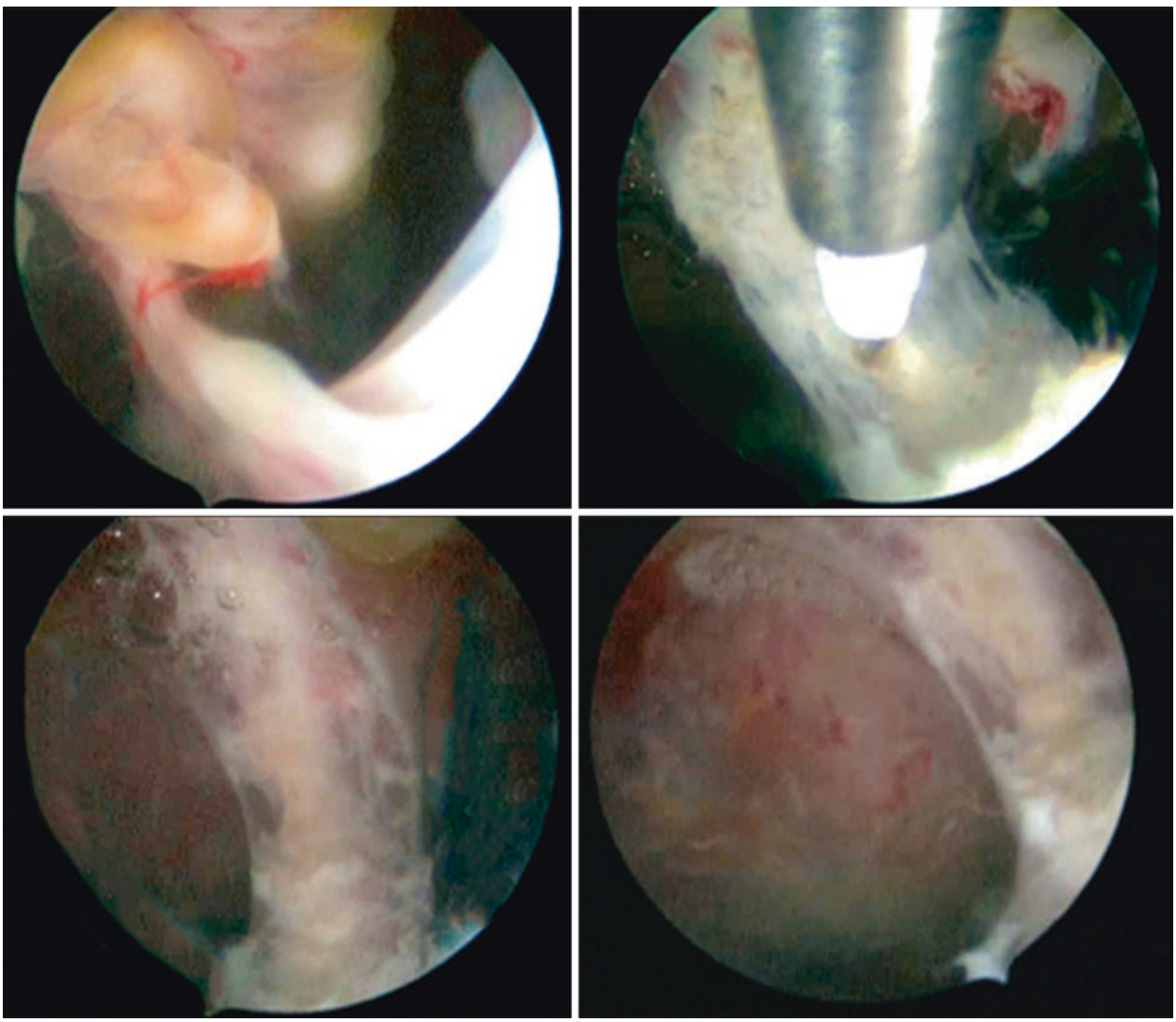


Photo 20.50 Photography sequence of the procedure

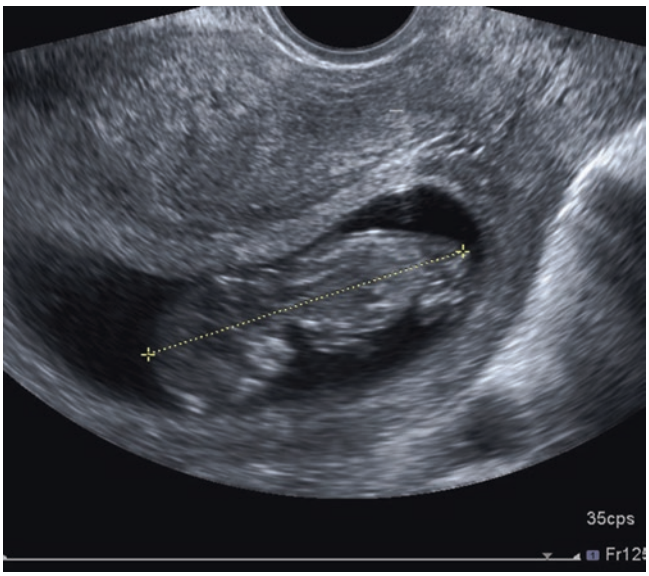


Photo 20.52 Detail of pregnancy in utero

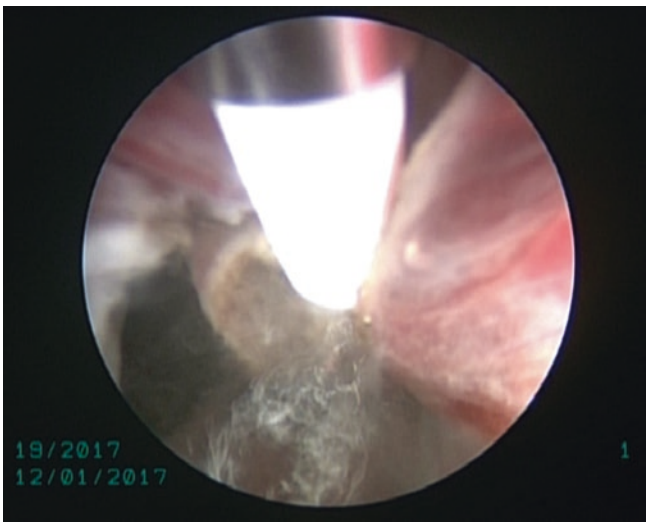


Photo 20.54 Beginning of the cut of the polyp pedicle with bipolar electrode

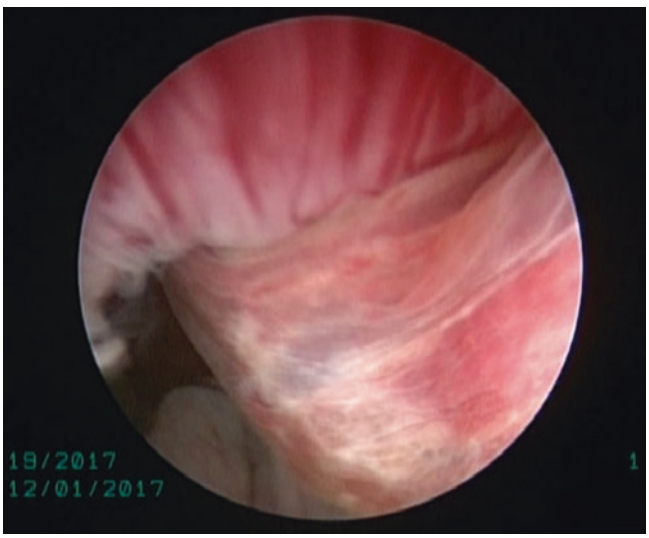


Photo 20.53 Hysteroscopic view of the base of the polyp

Photo 20.55 Detail of the pedicle cut

Photo 20.56 Close-up to the pedicle where the glands of the polyp pedicle can be seen

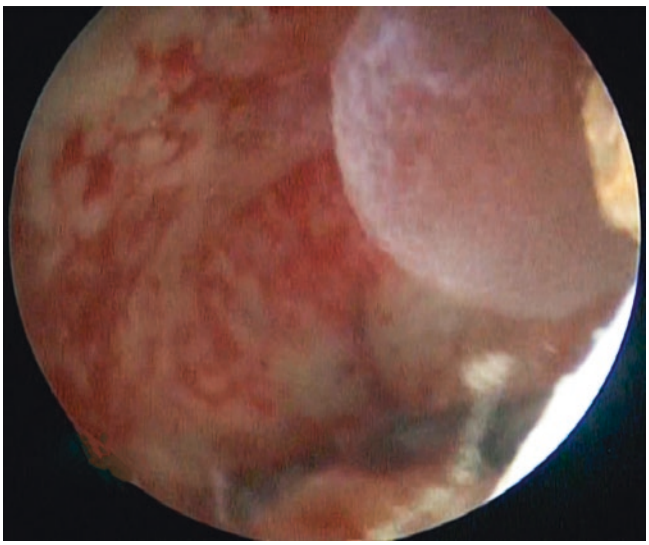


Photo 20.58 Intra-amniotic view where the yolk sac is observed and the thin dark line that suggests necrosis of the umbilical cord by thrombophilia

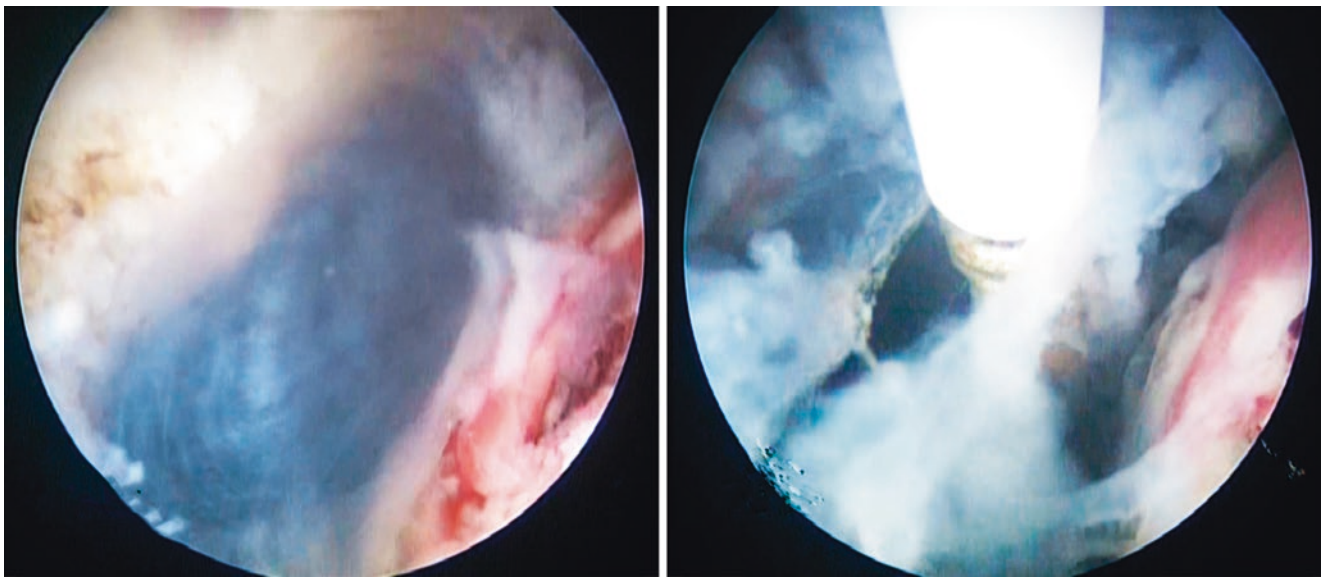


Photo 20.57 The gestational sac

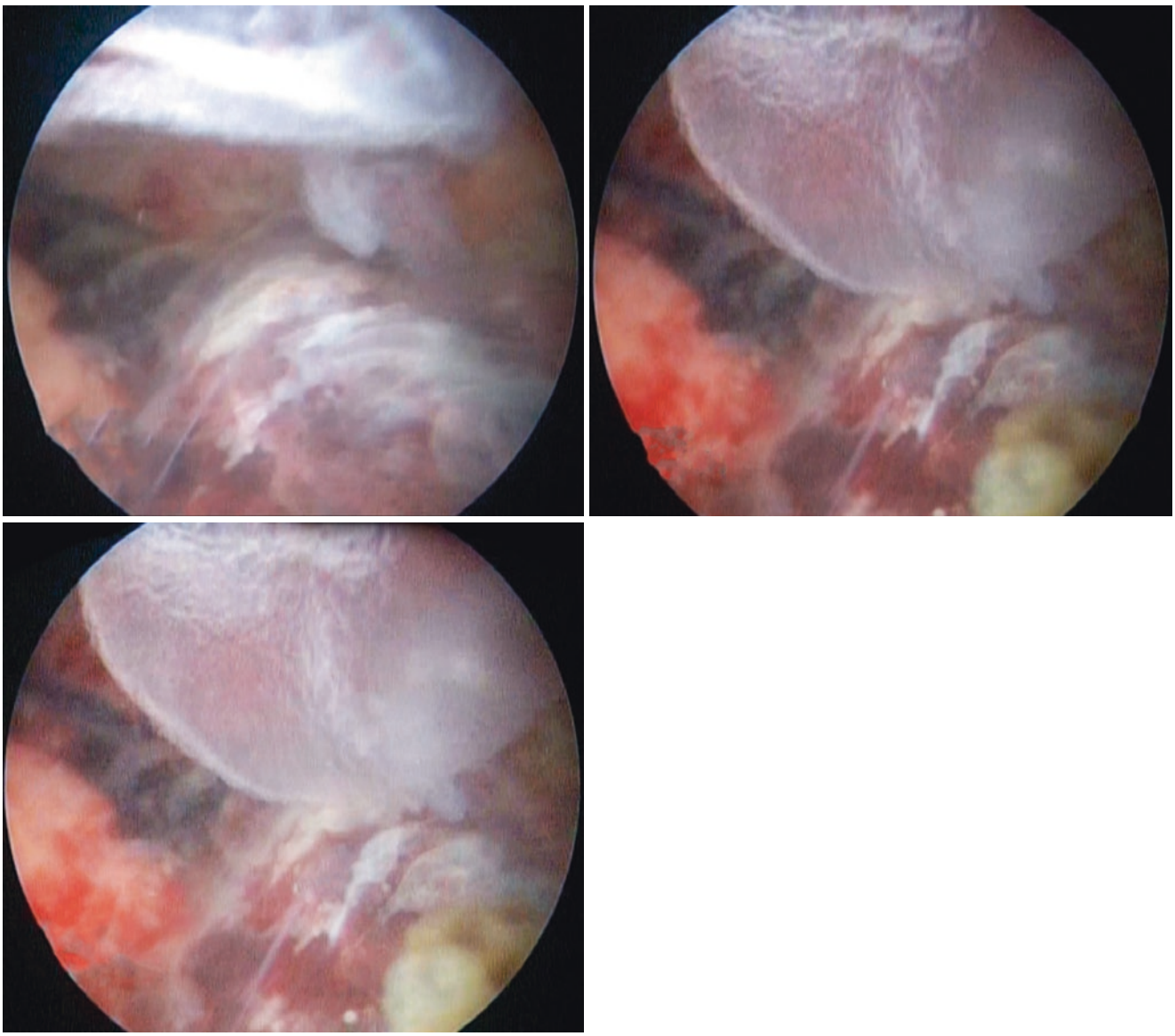


Photo 20.59 Procedure sequence

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Hysteroscopy and Contraception

21

Andreas L. Thurkow

21.1 Introduction

The relation between hysteroscopy and contraception consists of several fields.

The oldest and most common connection is in the transcervical and usually hysteroscopic sterilisation.

But hysteroscopy also plays a role in problems with various contraceptive methods: removal of lost or malpositioned IUDs, and removal of sterilisation devices.

And last but perhaps not least in the future is the option of placing long-acting contraceptive devices by hysteroscopy.

21.2 Hysteroscopic Sterilisation

As long as the history of hysteroscopy itself exists blind transcervical attempts have been undertaken to permanently block the uterine cavity or the fallopian tubes [1].

One of the earlier blind methods used electrocautery in order to obtain these results. In 1927 the first actual hysteroscopic sterilisation, using the same electrocautery method, was described. Unfortunately, the results were disappointing.

Later attempts with electro-, cryo-, or Nd-YAG laser coagulation were equally unsuccessful in achieving bilateral occlusion (in 15% up to a maximum of 60% of cases) [1–4].

Since hysteroscopy found its way as a routine diagnostic and interventional technique in the 70s and 80s of the last century even more methods have been tested, among which are several types of intratubal occlusion devices. All of these initial methods have been abandoned, either due to complications or due to lack of effectiveness or both [3, 5–7].

From 2003 to 2006, Chiroxia Ltd. (Dublin, Ireland) investigated the hysteroscopic application of a cyanoacrylate-based liquid polymer implant, in which the author of this chapter performed the study on explanted uteri (Figs. 21.1, 21.2, and 21.3).

Although the initial results were promising, the investors withdrew their support and the project was discontinued.

The first hysteroscopic sterilisation technique that made it to the market (CE mark in Europe, never FDA approved) was Ovabloc® (Figs. 21.4 and 21.5).

Clinical studies on Ovabloc had been performed as early as 1967 ([8, 9]).

Through a double-catheter system the two-component fluid siloxane mixture with a high viscosity is injected in

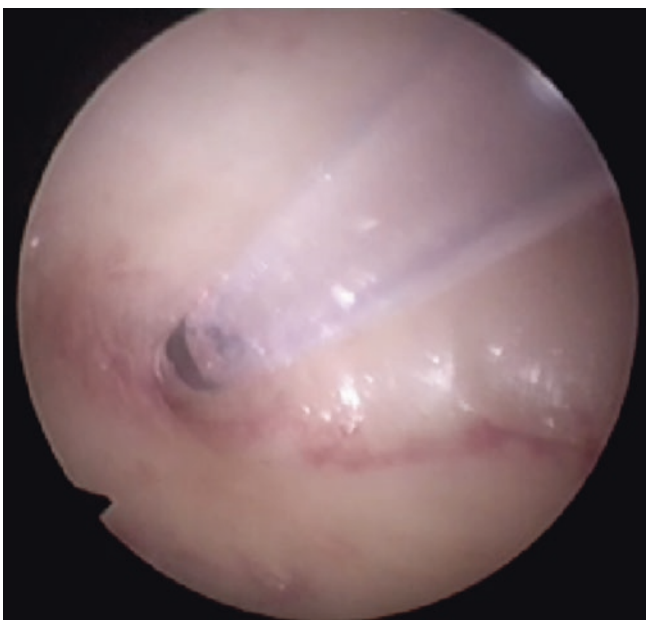

Fig. 21.1 Chiroxia® catheter inserted in right tubal os (explanted uterus)

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_21) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_21

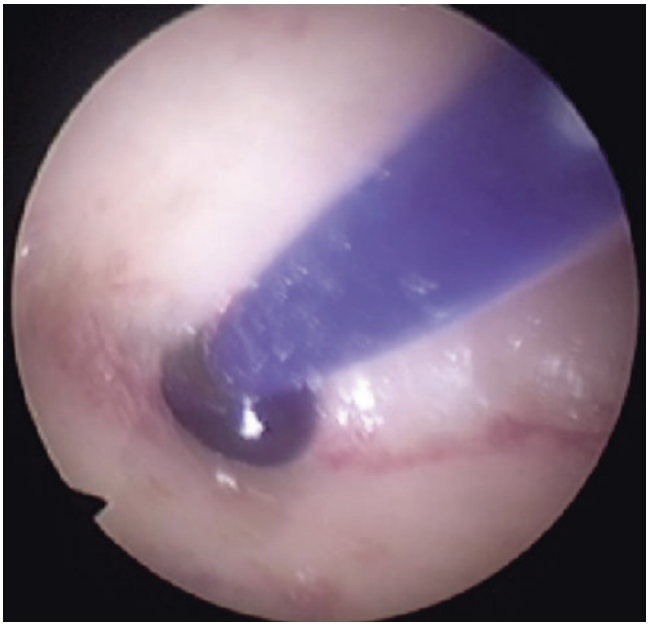

Fig. 21.2 Chiroxia® compound injected

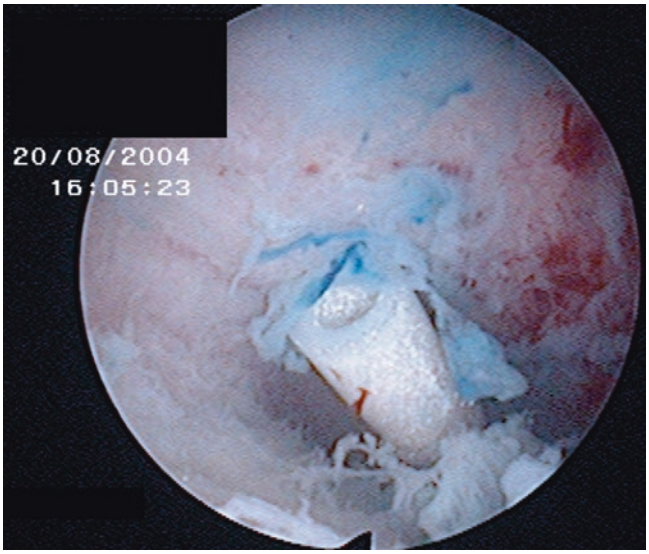

Fig. 21.4 Ovabloc® intrauterine tip after insertion and solidification. Note blue colouring of the endometrium by methylene blue used to ascertain correct positioning of the catheter and patency of the fallopian tube prior to insertion of the siloxane compound

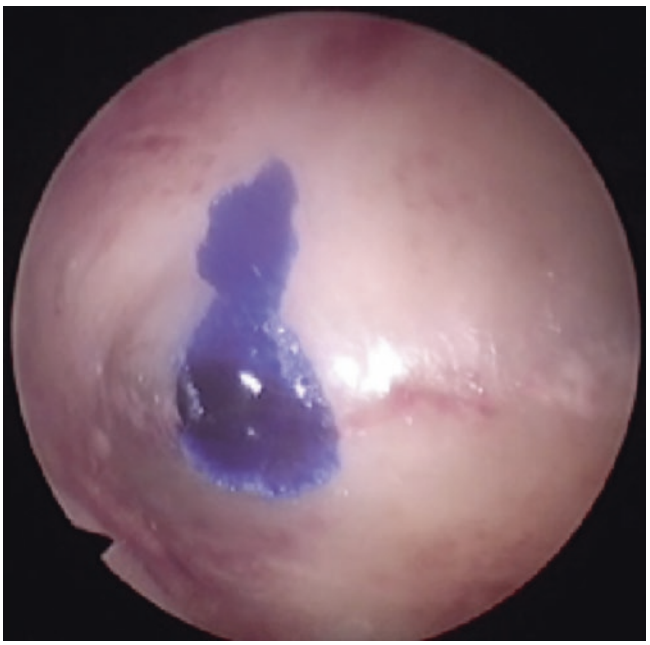

Fig. 21.3 Chiroxia® compound solidified after removal of catheter

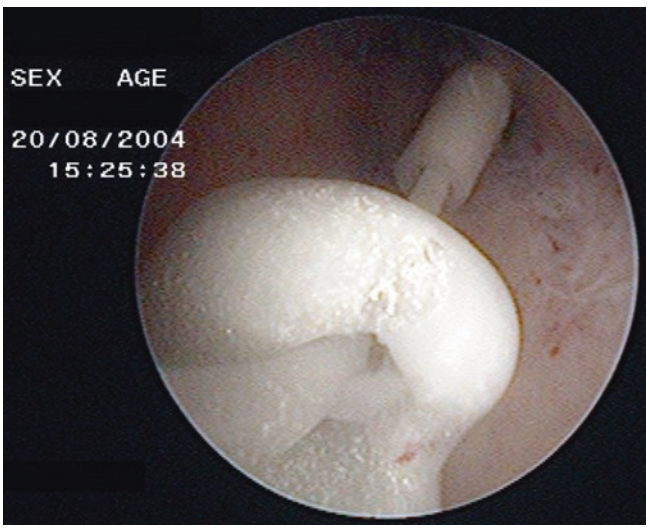

Fig. 21.5 Excessive siloxane reflux into the uterine cavity after Ovabloc® insertion that needs to be cut to prevent expulsion and abnormal uterine bleeding

the fallopian tubes, which cures within minutes and hereby causes occlusion of the tubal lumen. A specially designed siloxane obturator tip, which is pre-attached on the inner catheter, forms a complex with the intraluminal plug and causes sealing in the uterotubal junction (Fig. 21.4).

Around 2000 patients have been sterilised with this method in the Netherlands; the use of Ovabloc® declined after the introduction of Essure® and has virtually disappeared from the market after the introduction of Adiana®. A new version of the device has recently been developed (Ovalastic®), with an easier instillation process and a compound that is stable under room temperature (Ovabloc® required storage at −20 °C). The tip of Ovalastic® is no longer made of siloxane as was the case with Ovabloc®, but of platinum (Figs. 21.6, 21.7, 21.8, and 21.9).

Only few clinical data of actual procedures are available yet, the only procedures having been performed either by the author or under his supervision. Further studies are needed to evaluate the clinical relevance of the method.

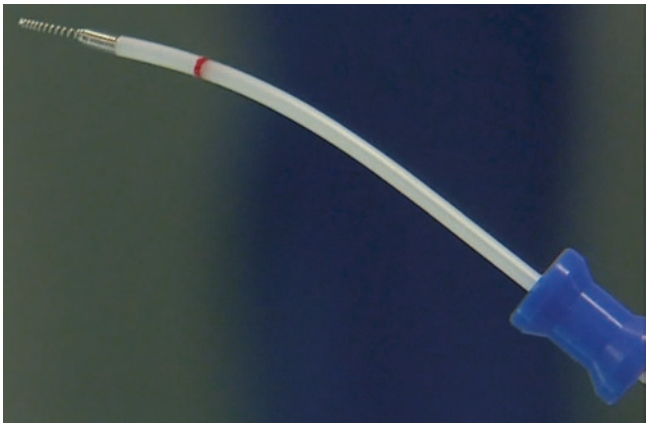

Fig. 21.6 Ovalastic® catheter with platinum tip attached prior to insertion

Fig. 21.7 Ovalastic® gun used to insert the siloxane compound into the fallopian tube under pressure

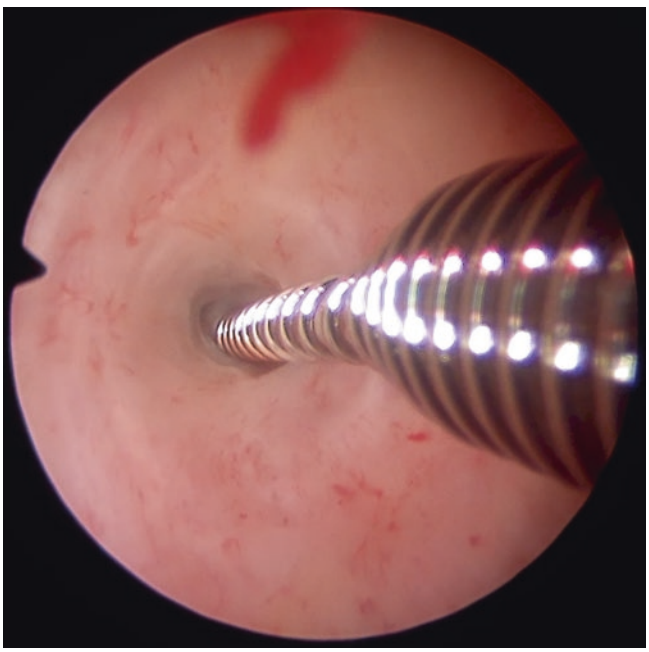

Fig. 21.8 Insertion of the Ovalastic® tip into the left tubal os prior to injection of the siloxane compound

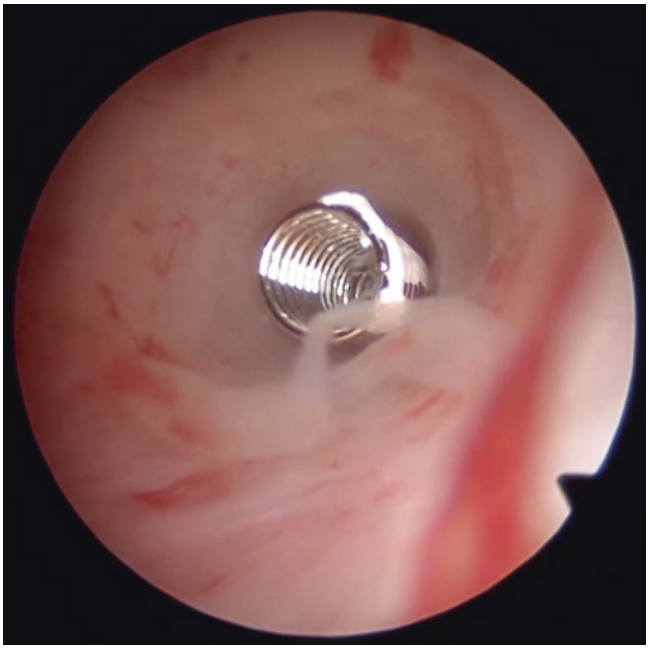

Fig. 21.9 Intrauterine part of the Ovalastic® platinum tip attached to now solidified siloxane in the fallopian tube

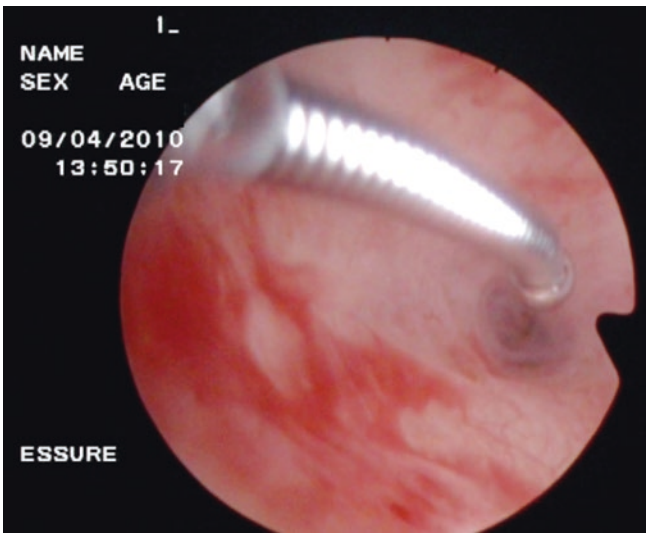

Fig. 21.10 Essure® device just before insertion in the right tubal os

The most successful hysteroscopic sterilisation system worldwide has been the Essure®, which received CE mark in 2001 and FDA PMA approval in 2002.

The Essure® micro-insert (Bayer AG, formerly Conceptus Inc.), initially called STOP, was a dynamically expanding micro-coil with polyethylene terephthalate (PET) fibre wound in and around the inner coil. It was placed through a 5 Fr working channel of a hysteroscope in the intramural section of the fallopian tube, in which it anchored itself by expansion of the coil (Figs. 21.10, 21.11, 21.12, and 21.13). The PET fibres subsequently caused a fibrotic reaction, which

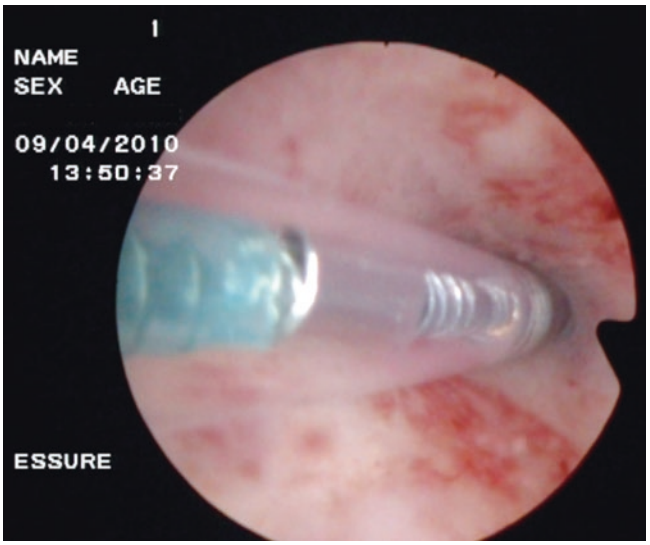

Fig. 21.11 Essure® catheter in place before retraction of the catheter and release of the device

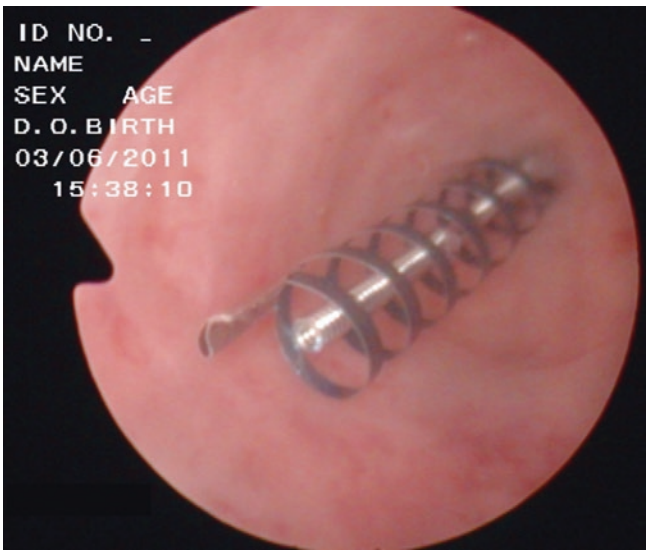

Fig. 21.13 Correctly placed Essure® device with six coils of the outer nitinol part trailing into the uterine cavity

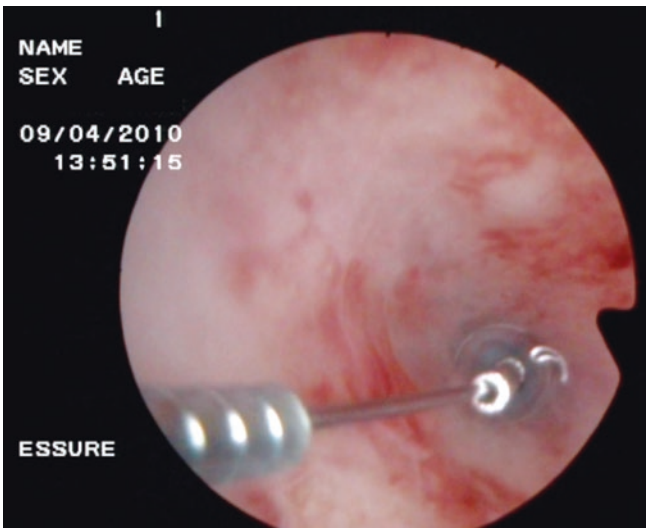

Fig. 21.12 Essure® device in place after deployment and release of the catheter

Fig. 21.14 Essure® device in place 8 years after insertion

rendered an additional anchoring and obstructing effect. The method proved to be effective and for an experienced hysteroscopist the technique was simple and fast [10, 11].

The mean procedure time was less than 15 min, partly due to the fact that most cases can be completed without anaesthesia by vaginoscopic approach [12].

On second-look hysteroscopy many years after insertion the device may be intact (Fig. 21.14), hardly or no longer visible due to fibrotic closure of the tubal os (Fig. 21.15), or covered with calcification (Fig. 21.16).

More than 900,000 procedures have been performed worldwide, until the manufacturer withdrew the device from the market after a drop in sales probably related to the increasing number of reports of late adverse effects (see the chapter on complications; Figs. 21.17 and 21.18). The last country to discontinue Essure sales was the USA on the 31st December 2018.

In 2009, another hysteroscopic sterilisation system, Adiana® (Hologic Inc.), received CE marking and was approved by the FDA later in the same year [13].

The device consisted of a 1.5 × 3.5 mm silicone matrix that was introduced in the intramural portion of the fallopian tube after superficial radiofrequency coagulation of the

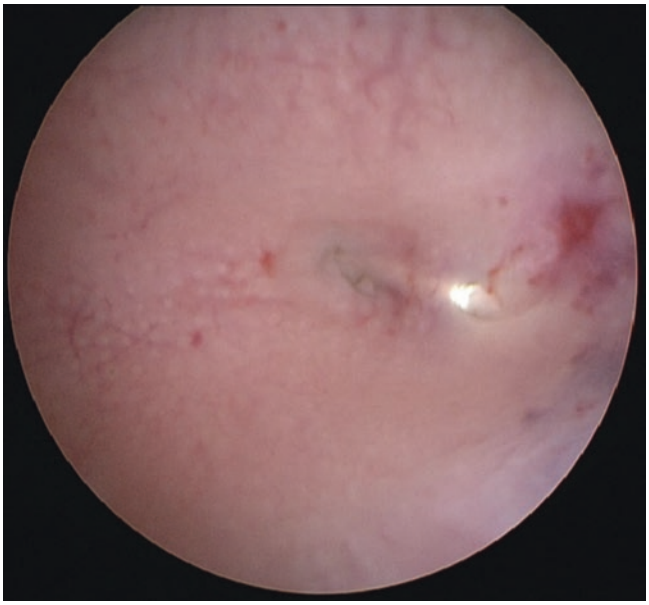

Fig. 21.15 Essure® device embedded in the tubal cornua and covered with endometrium

Fig. 21.16 Essure® device years after insertion before removal for late adverse effects with calcification (partly responsible for symptoms?)

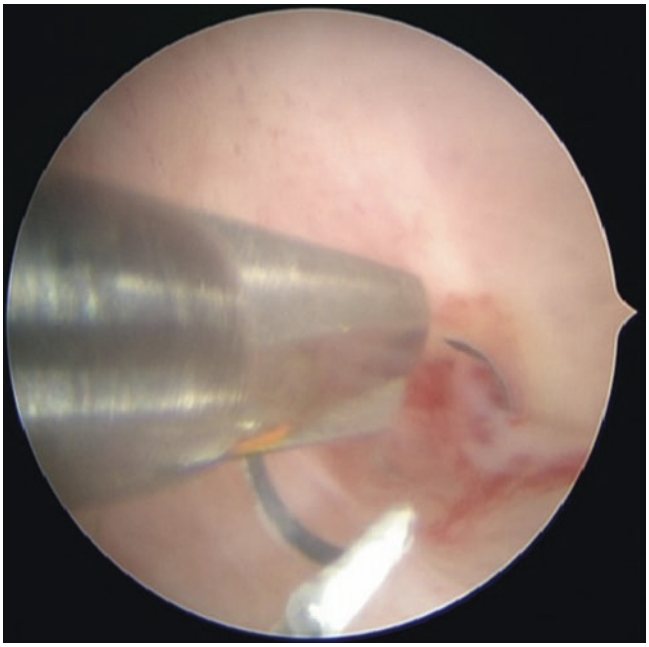

Fig. 21.17 Cutting of the terminal (4th) marker before laparoscopic removal of the entire Essure® device to prevent fragmentation during laparoscopic extraction

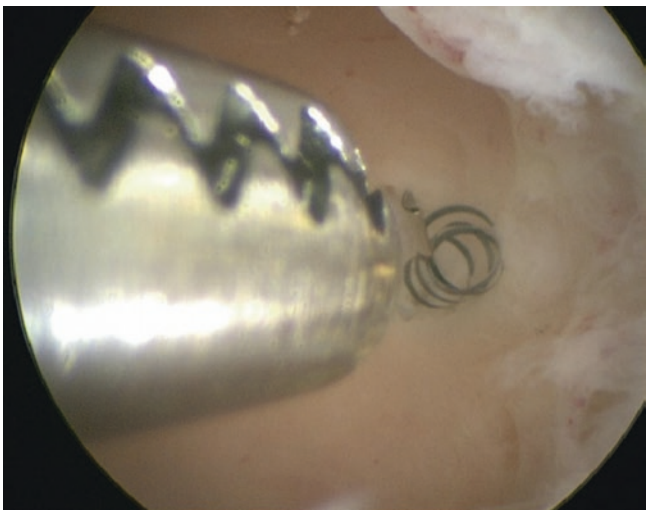

Fig. 21.18 Removal of the cut terminal marker (see Fig. 21.17)

tubal mucosa (3 W during 60 s for each side) to stimulate fibrotic tissue ingrowth into the matrix (Figs. 21.19, 21.20, and 21.21).

The system included a dedicated generator that controlled the correct positioning and delivered the energy for the coagulation.

Although the devices were visible with vaginal ultrasound, the confirmation test required was a HSG after 3 months to ensure blockage of the fallopian tubes. The initial version of the matrix was not radiopaque; in 2011, a radiopaque version was introduced in the European market, which added significantly to the reliability of the confirmation test. Two hundred procedures have been carried out in the Netherlands, half of which by the author of this chapter. Twenty-nine thousand and five hundred procedures have been performed worldwide, until the Hologic company decided to withdraw the product from the market in May 2012.

Several alternative methods are in the pipeline and may be introduced in the future.

Among these are the Altaseal® device (Altascience Ltd.) and the ZRO Operculum®. It is not clear what the current

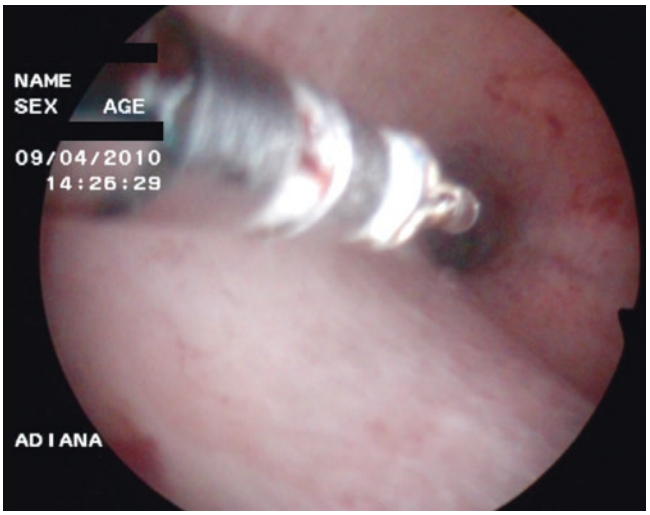

Fig. 21.19 Insertion of the Adiana® catheter into the right tubal os

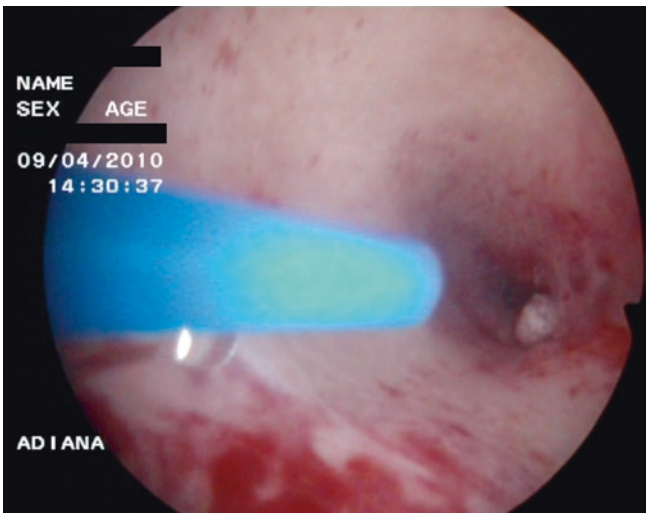

Fig. 21.21 Adiana® device in place in the tubal os after release by the catheter

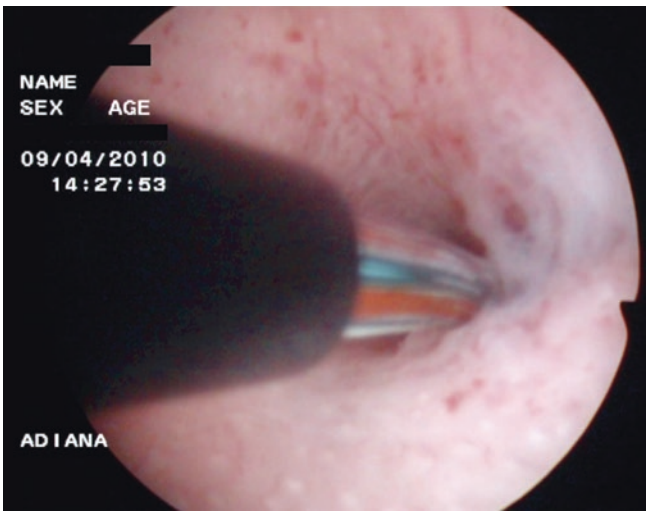

Fig. 21.20 Superficial coagulation of the tubal mucosa during 60 s to ensure ingrowth of fibrotic tissue into the matrix of the Adiana® device (note the electric wiring in the catheter)

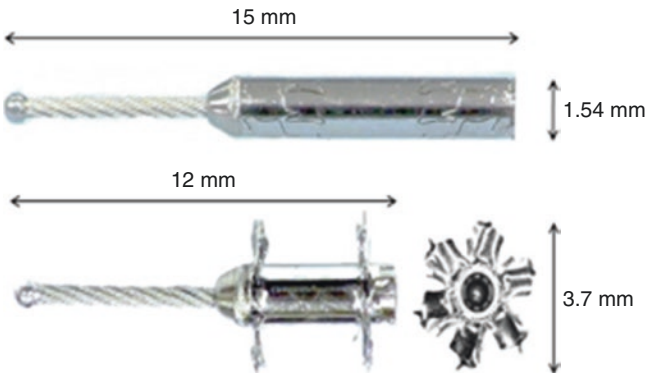

Fig. 21.22 Details and dimensions of the Altaseal® device before and after deployment (courtesy of Altascience ltd.)

status of the latter device is; as far as known to the author it has not been subject to clinical studies yet.

The Altaseal® device consists of a high-grade stainless steel instant blocking device of the fallopian tube that does not depend on tissue ingrowth and therefore might have the advantage of immediate closure (Figs. 21.22, 21.23, 21.24, 21.25, and 21.26). The peri-hysterectomy study performed by the author of this chapter [14] and a clinical pilot study in Ireland [15] have been promising in this respect. In the Irish clinical study eventually 22 patients have been sterilised; all had an immediate closure of the fallopian tubes and all procedures were well tolerated with an average duration of 5 min, and a follow-up period of 3 years. The FDA multi-centre pivotal trial has been performed in three centres in the Netherlands and one centre in Ireland with 83 patients [16]. Of these 78 patients underwent an attempt to be sterilised and 66 are now relying on the procedure. In nine patients (11.5%) misplacement of the devices occurred, probably mainly due to the design that was suspected to be the main cause of this complication. The confirmation test for proper placement to date has been vaginal ultrasound (Fig. 21.27), but it is expected that in the future a confirmation test will be no longer required, on the basis of the abovementioned data. A new trial with a modified design has therefore been submitted to the Irish and Dutch regulatory bodies and has started in 2018.

Yet other devices are bound to be developed, in view of the interest for minimal invasive sterilisation options, especially in the developing countries, where the devices that have been on the market have never shown a large penetration due to the costs of the material.

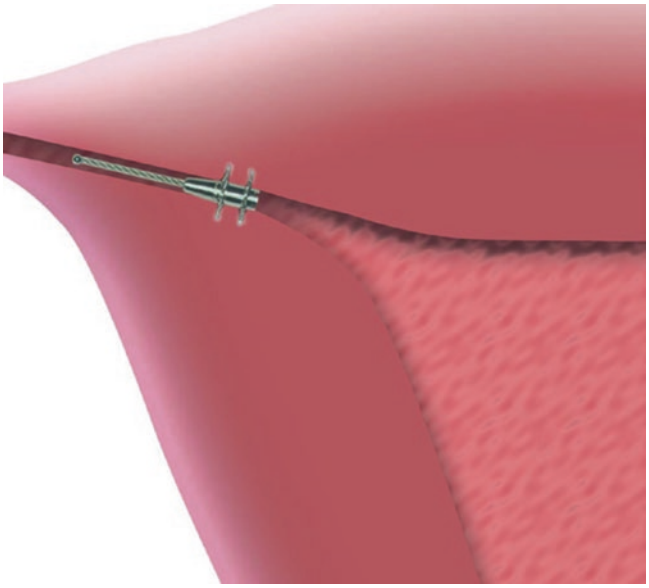

Fig. 21.23 Graphic illustration of an Altaseal® device in the intramural portion of the fallopian tube

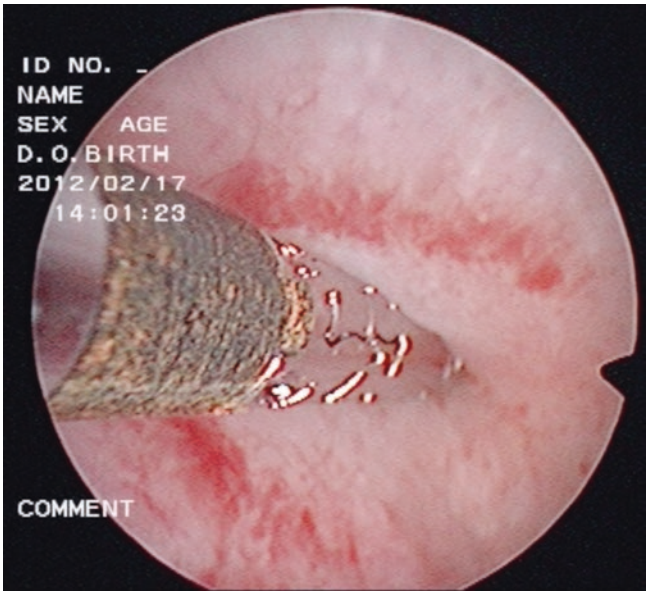

Fig. 21.25 Altaseal® device insertion in the right tubal os before deployment

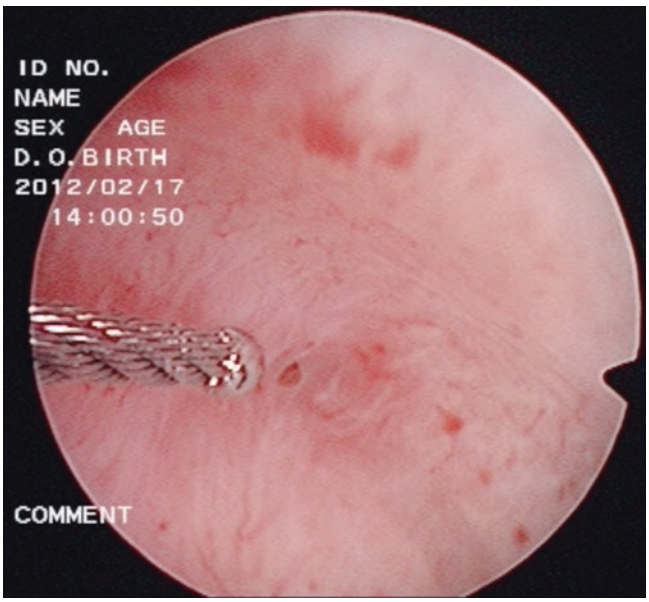

Fig. 21.24 Altaseal® device just before insertion in the right tubal os

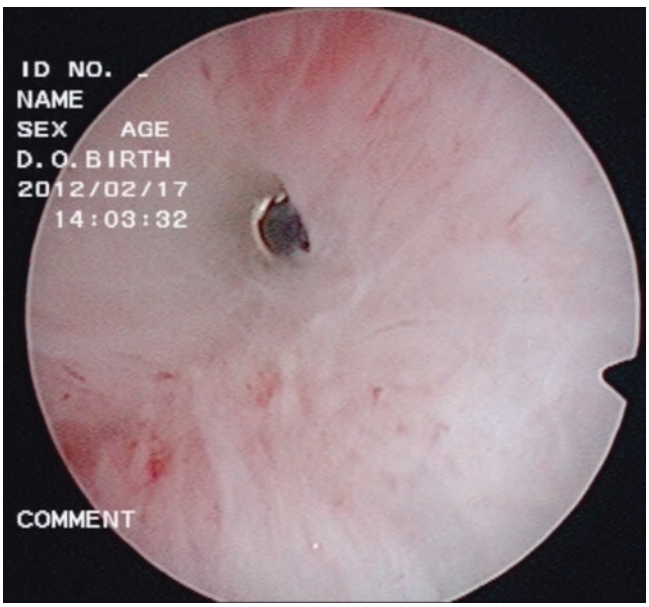

Fig. 21.26 Correct position of the Altaseal® device in the right tubal os after deployment and detachment

21.3 Hysteroscopic Problem-Solving in Contraception

Hysteroscopy has been used as a tool to solve many problems related to contraceptive methods and devices, although literature on the subject is scarce and not very recent [17–19]. Given the fact that it is usually stated as one of the main indications for therapeutic hysteroscopy [20], it seems that this indication is underreported.

- Retrieval of intrauterine devices (missing or no strings, misplacement, partial perforation, etc.; Figs. 21.28, 21.29, 21.30, 21.31, 21.32, 21.33, and 21.34)
- Repositioning of IUDs (malplacement, partial perforation, etc.; Figs. 21.35 and 21.36)
- Removal of dislodged or expelled hysteroscopic sterilisation devices (Essure®, Adiana®, Ovabloc®, etc.)

Fig. 21.27 Ultrasound confirmation of correct positioning of the Altaseal® device in the intramural portion of the left fallopian tube. Note the alignment with the cornual area and the deployment of the two wings in the uterine wall

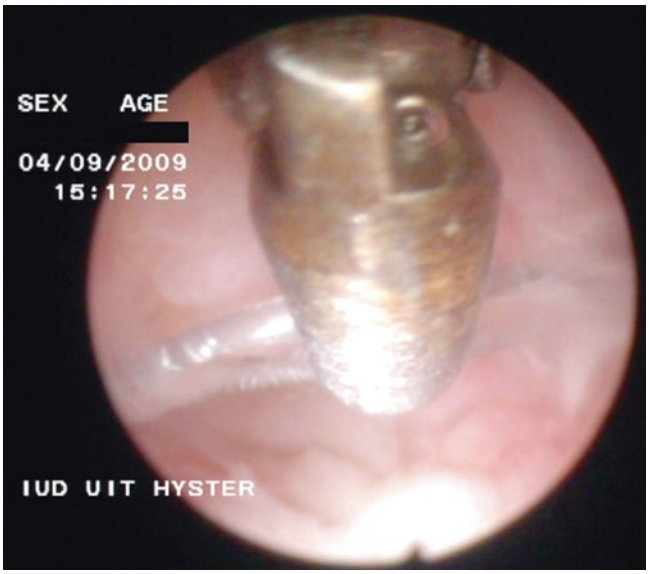

Fig. 21.28 Hysteroscopic removal of an IUD after retrieval of missing threads (folded back in the cervical canal)

21.4 Hysteroscopic Placement of Long-Acting Contraceptive Devices

Another hysteroscopic approach to contraception, albeit not permanent, is ReLARC®, which is a reversible long-acting reproductive control method that basically consists of hysteroscopic placement of a frameless copper IUD (also known as Gynefix®, Figs. 21.37, 21.38, 21.39, 21.40, and 21.41) that is anchored in the uterine fundus [21].

The duration of action is up to 10 years (currently 5 years for Gynefix®).

Clinical studies are in preparation [21].

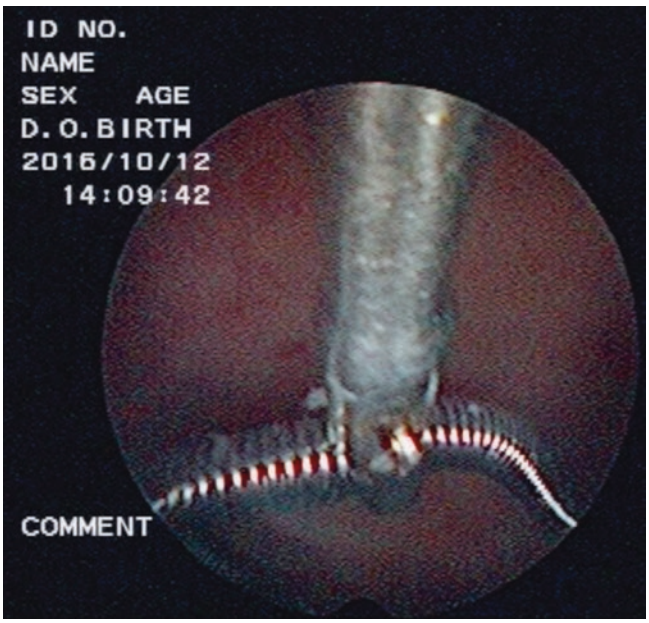

Fig. 21.29 Hysteroscopy removal of a (Chinese) threadless IUD

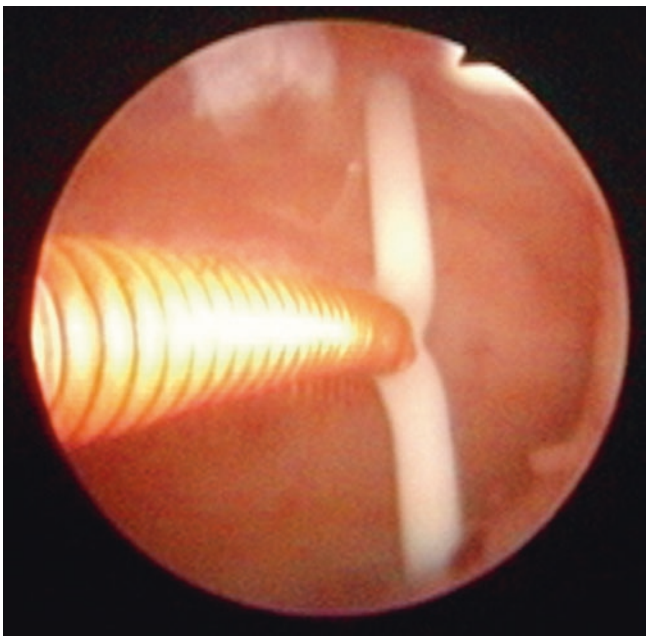

Fig. 21.30 Partial perforation of a Mirena® into the uterine wall causing bleeding and pain

21.5 Notes

The text in this chapter is an updated, but shortened, version of an earlier publication: Thurkow AL. Hysteroscopy and Contraception: an overview. In: Hysteroscopy. Andrea Tinelli, Luis Alonso Pacheco, Sergio Haimovich, Editors. ISBN 978-3-319-57558-2 ISBN 978-3-319-57559-9 (eBook) https://doi.org/10.1007/978-3-319-57559-9 © Springer International Publishing AG 2017

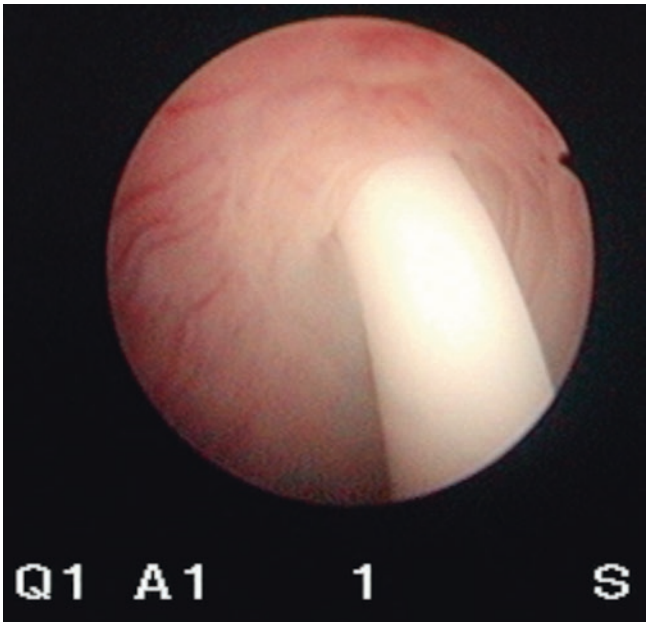

Fig. 21.31 Close-up image of Fig. 21.30

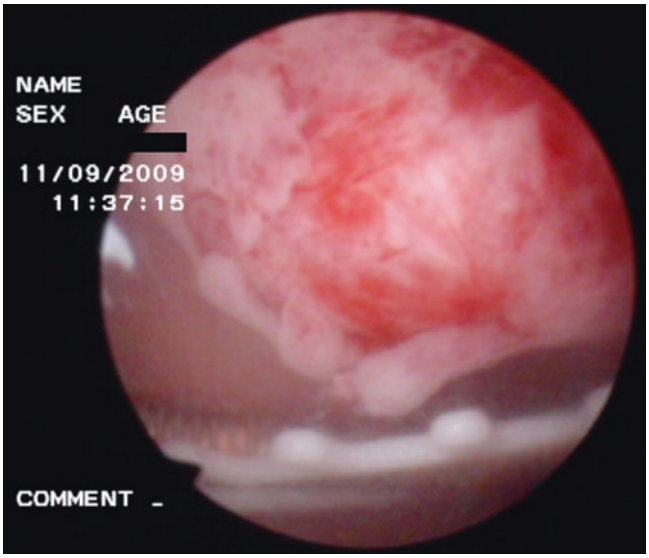

Fig. 21.33 Close-up image of Fig. 21.32

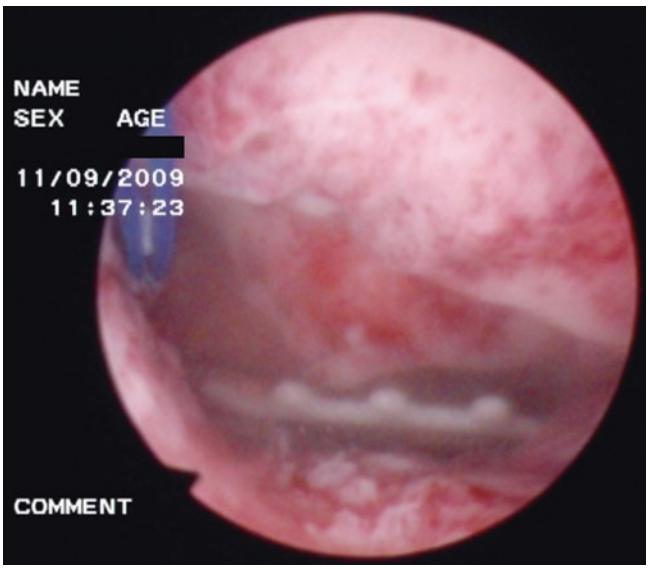

Fig. 21.32 Dislocation of a Multiload® copper IUD in the presence of (or caused by?) a submucous fibroid in the anterior wall. The IUD has rotated 90° with the vertical stem now lying in a horizontal position in the fundal area (string attachment in the right tubal cornua)

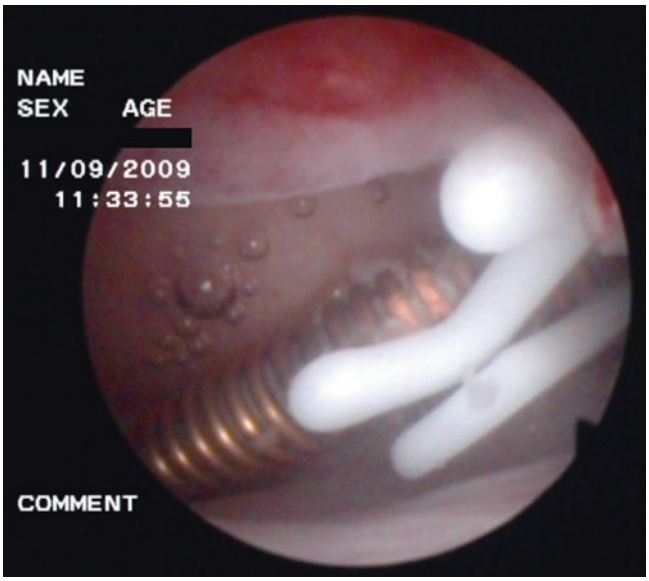

Fig. 21.34 Further close-up image of Figs. 21.32 and 21.33

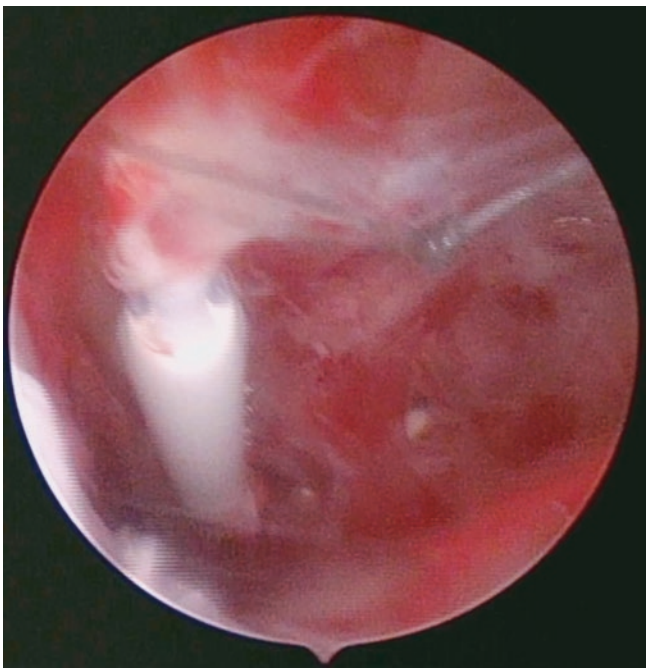

Fig. 21.35 Mirena® embedded in adhesions in the fundal area, possibly an explanation of persistent pain and bleeding after insertion

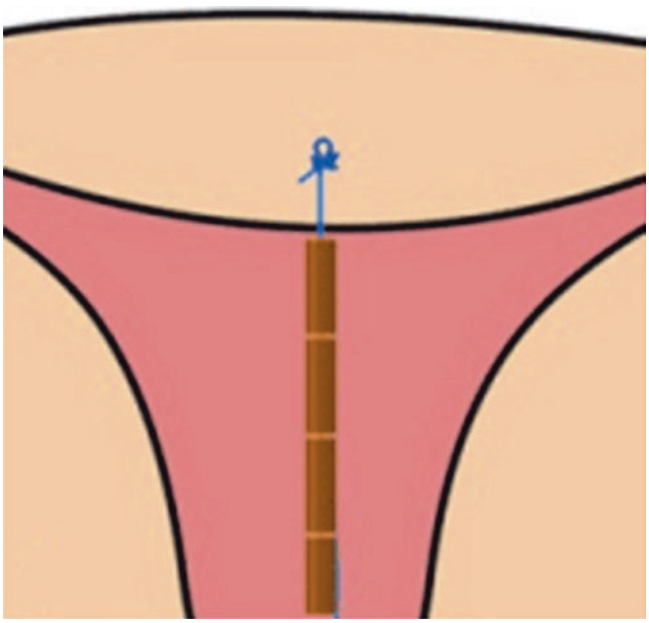

Fig. 21.37 Graphic illustration of frameless Gynefix® intrauterine device anchored in the fundal myometrium (courtesy of Dr. Th. Hasskamp)

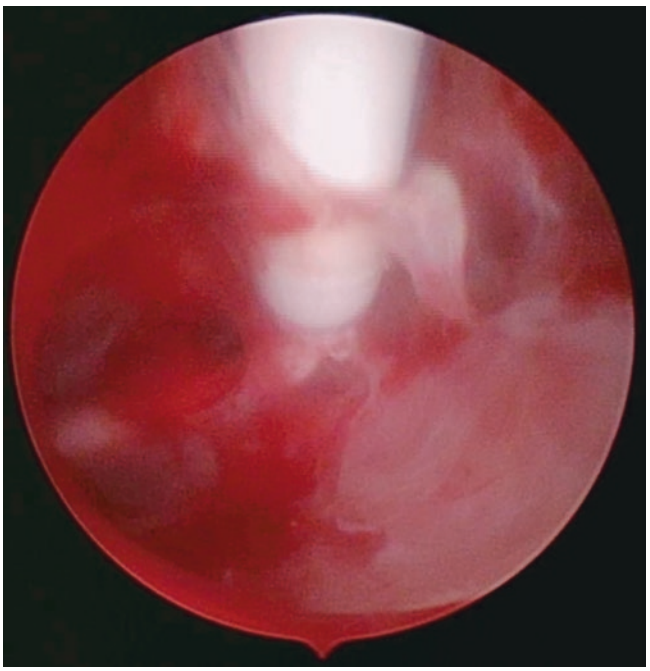

Fig. 21.36 Close-up image of Fig. 21.35

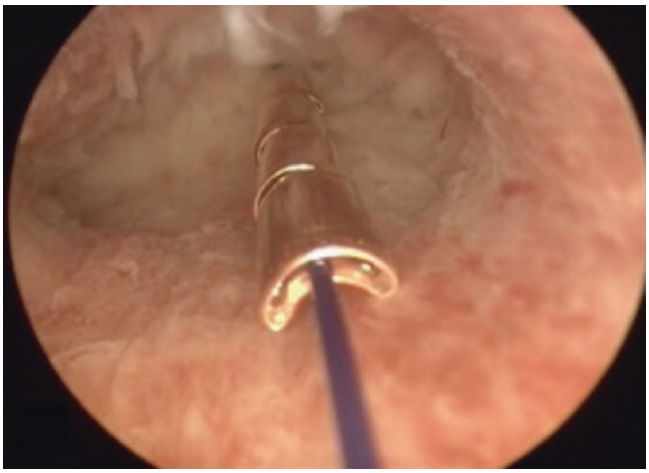

Fig. 21.38 Hysteroscopic view of a Gynefix® IUD after placement (courtesy of Dr. Th. Hasskamp)

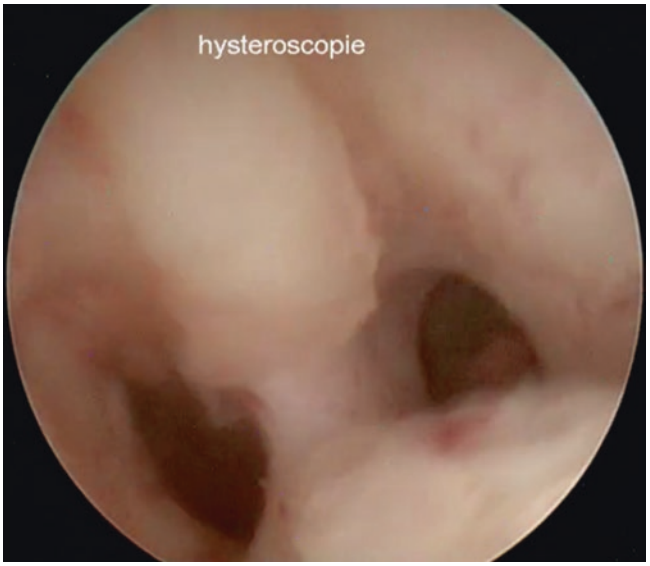

Fig. 21.39 Hysteroscopic view of a septate uterus of a patient after recurrent expulsions of various intrauterine devices, who explicitly requested a hysteroscopic septum resection and insertion of a Gynefix® device

Fig. 21.41 Same patient as in Figs. 21.38 and 21.39 after insertion under hysteroscopic view of a Gynefix® intrauterine device in the remaining fundal area after successful septum resection. Ultrasound control confirmed placement of the anchoring knot in the mid-myometrial area of sufficient remaining tissue in the uterine fundus

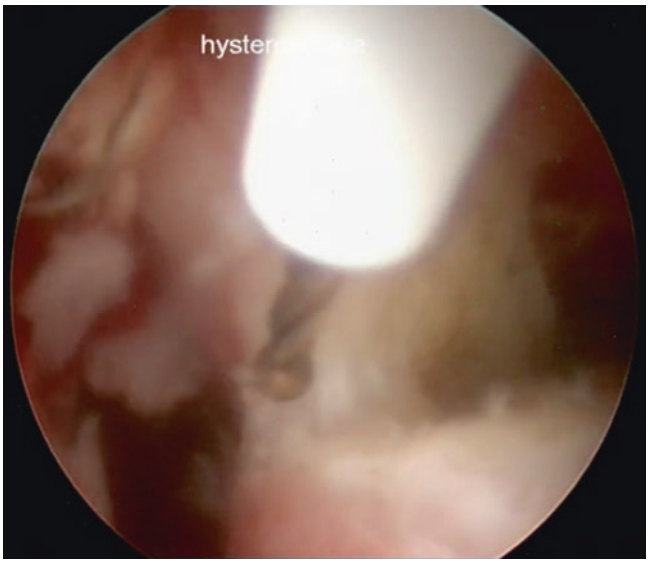

Fig. 21.40 The same patient as in Fig. 21.38 during septum resection with a bipolar Versapoint® twizzle vaporisation device

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Hysteroscopy and Tubal Pathologies

22

Shlomo B. Cohen and Gennario Raimondo

22.1 Background

22.1.1 The Fallopian Tube

The main function of the uterine tubes is to assist in the *transfer* and *transport* of the fertilized oocyte from the site of fertilization in the tubal ampulla to the uterus.

The two fallopian tubes are about 10 cm long and they are located within the mesosalpinx. The fallopian tubes consist of four main parts, from medial to lateral (Fig. 22.1) [1, 2]:

- *The intramural (interstitial)* part, which is located within the myometrium of the uterus, is 1 cm long and 0.7 mm wide.
- *The isthmus* is 3 cm long and between 1 and 5 mm wide.
- *The ampulla* is the longest part of the tube. It has a diameter of 1 cm at its widest point and is 5 cm long.
- *The infundibulum*, which is the distal end of the tube: It is funnel shaped and opens into the peritoneal cavity at the abdominal ostium. Fingerlike mucosal projections are attached to the distal end of the infundibulum and are referred to as *fimbriae*. The longest of the fimbriae, *the ovarian fimbria*, attaches to the superior aspect of each ovary.

Arterial supply involves both the uterine and ovarian arteries. The uterine artery supplies the medial two-thirds of the tube, while the lateral third is supplied by the ovarian artery.

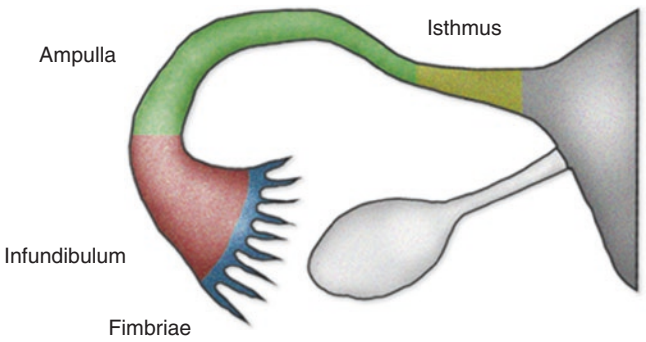

Fig. 22.1 The ovarian fimbria attaches to the superior aspect of each ovary

Venous drainage drains the medial two-thirds of the fallopian tubes into the internal iliac vein whereas the pampiniform plexus drains the lateral two-thirds. The pampiniform plexus drains into the ovarian veins, which in turn drain into the renal vein on the left and the inferior vena cava on the right (Fig. 22.2).

Lymphatic Drainage: Lymph is also drained by both ovarian and uterine vessels, which drain into the para-aortic and internal iliac lymph nodes, respectively.

Innervation: The fallopian tubes are innervated by both the sympathetic and parasympathetic nervous systems.

Histology: The walls of the fallopian tubes consist of three main layers:

- *Tubal mucosa:* It consists of longitudinal folds of columnar epithelium made of ciliated (in the distal portion of the tubes), non-ciliated secretory (in the proximal portion of the tubes) and intercalated cells. The secretion of these epithelium provides a nutrient for the fertilized ovum.
- *Tubal muscularis:* It is arranged into two layers whose innervation results in peristaltic contractions which assist in propulsion of the fertilized ovum.
- *Tubal serosa:* It is an outer covering layer of the muscularis layer [3].

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_22) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_22

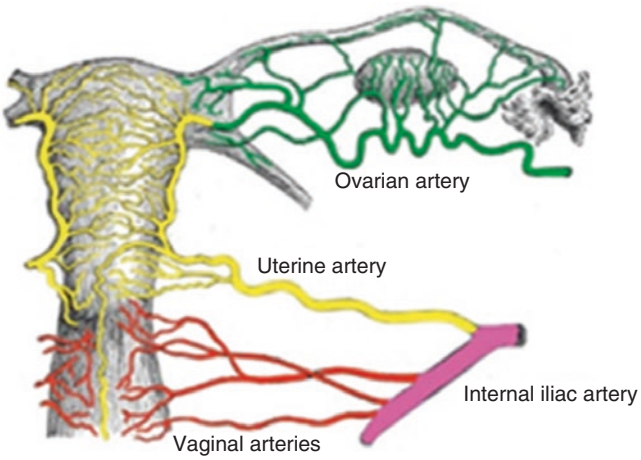


Fig. 22.2 The pampiniform plexus drains into the ovarian veins, which in turn drain into the renal vein on the left and the inferior vena cava on the right

Embryology: The fallopian tubes develop from the paramesonephric or Müllerian ducts (generated from the mesoderm).

22.2 Physiology

The fallopian tubes are involved in the transport of the ovum from the ovary to the uterus and once fertilization takes place the tubes also provide nourishment for the fertilized ovum. The most amazing of the multiple functions of the fallopian tube is that the tube first directs the sperm towards the ampulla and then returns the fertilized egg to the uterus. The fallopian tube has a rhythmic peristalsis and, based on correlation between tubal anatomy and physiology (Fig. 22.3) [4], we can speculate that the different layers have different roles:

- *Myosalpinx*: ovum transport
- *Innervation*: might function as adrenergic sphincter
- *Mucosa*: provides a supportive environment
- *Uterotubal junction*: distal isthmus is not critical to reproduction
- *Fimbria*: special role of ovum pickup

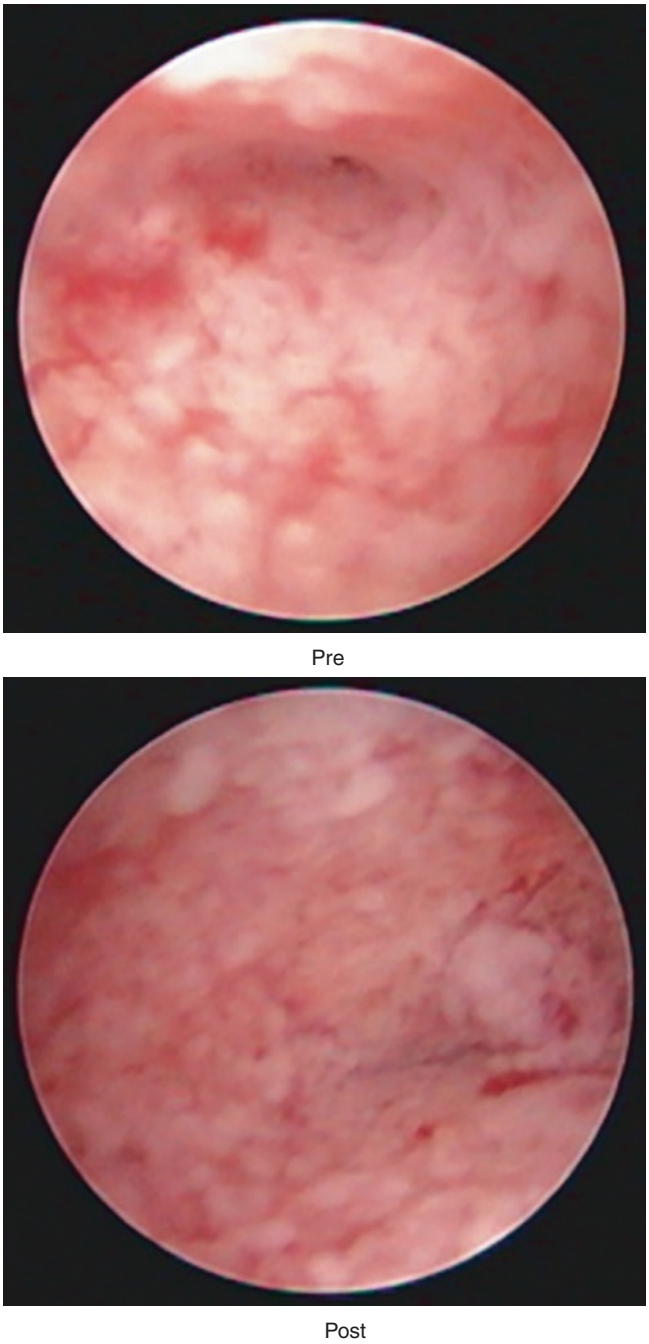


Fig. 22.3 The fallopian tubes

22.3 Tubal Occlusion Due to Infectious Diseases

Salpingitis is the inflammation of the fallopian tube, most commonly caused by infection. Acute salpingitis is often used synonymously with *pelvic inflammatory disease* (PID) because it is the most common form of PID and because the most common and serious long-term sequelae of PID involve the tubes. The main risk factor for acquiring acute salpingitis is sexually transmitted diseases (STDs) [5–7].

The microorganisms most frequently causing the infection are:

- *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (both most frequent pathogens), *Gardnerella vaginalis*, *Escherichia coli*, *Haemophilus influenzae*, *group B beta-hemolytic streptococci*, *non-hemolytic streptococci*, *Prevotella bivia*, *Bacteroides species*
- *Peptostreptococcus species*, *Mycoplasma hominis*, *Ureaplasma urealyticum*

Salpingitis is believed to be an ascending infection, mainly due to cervical and uterine instrumentation; hormonal changes during menses; retrograde menstruation favoring ascent to the fallopian tubes; and virulence factors of the microorganism itself.

22.3.1 Clinical Presentation and Diagnosis

The clinical presentation of salpingitis is highly diverse, ranging from asymptomatic to severe pelvic pain to diffuse peritonitis to, rarely, life-threatening illness [8].

The criteria for clinical diagnosis of PID are:

- Uterine tenderness, adnexal tenderness, cervical motion tenderness, oral temperature greater than 38.3 °C (>101 F), presence of abundant numbers of WBC on a wet mount elevated ESR and/or C-reactive protein levels, tubo-ovarian abscess (TOA) or thickened fluid-filled tubes with or without free fluid on ultrasonography or other imaging techniques, laparoscopic findings

IUDs should sometimes be removed in patients diagnosed with PID, dependant on the clinical condition of the patient.

The likelihood that a patient with acute salpingitis will develop *chronic pelvic pain* (20%) is four times that of patients without a pelvic infection (5%).

22.4 Tubo-Ovarian Abscess

TOA is one of the major and serious complications of acute salpingitis and occurs in up to 15% of women with PID [9].

22.5 Salpingitis Isthmica Nodosa

Salpingitis isthmica nodosa (SIN) or tubal diverticulum is a nodular thickening of the narrow part of the uterine tube. Fallopian tube epithelium will be outpouching into tubal wall. In severe cases, lumen may be completely obstructed. It may also be associated with endosalpingiosis. The clinical significance of SIN relies on its strong association with infertility and ectopic pregnancy [10, 11].

22.6 Endosalpingiosis

Endosalpingiosis refers to the presence of tubal epithelium outside the fallopian tubes [12].

The pathogenesis of endosalpingiosis is similar to that of endometriosis.

22.7 Ectopic Pregnancy

Ectopic pregnancy is a leading cause of pregnancy-related death during the first trimester.

The major cause of ectopic pregnancy is acute salpingitis, accounting for 50% of cases. Other causes are related to mechanical defect in the ciliary epithelium function, and infertility treatments [13].

22.8 Fallopian Tube Carcinoma

In the past it was believed to be rare. Some investigators have demonstrated precursor cancerous lesions in the fallopian tube (tubal in situ carcinoma [TIC]) and have speculated that many advanced serous "ovarian cancers" may have originated from the tubes rather than the ovary [14, 15].

22.9 Miscellaneous Reasons for Proximal Tubal Occlusion

- Polyps (Fig. 22.4)
- Peritubal adhesions (Figs. 22.5–8)
- Retained placenta at the fallopian tubal orifice (Fig. 22.9)
- Foreign bodies (Fig. 22.10)

22.9.1 Miscellaneous Tubal Images

- Enlarged tubal orifice in hydrosalpinx (Figs. 22.11–13)
- Tubal orifice scarring (Fig. 22.14)
- Open tubal orifice (Fig. 22.15)
- Tubal occlusion supported by HSG (Fig. 22.16)
- Tubal imagine in case of uterine septum (Fig. 22.17)

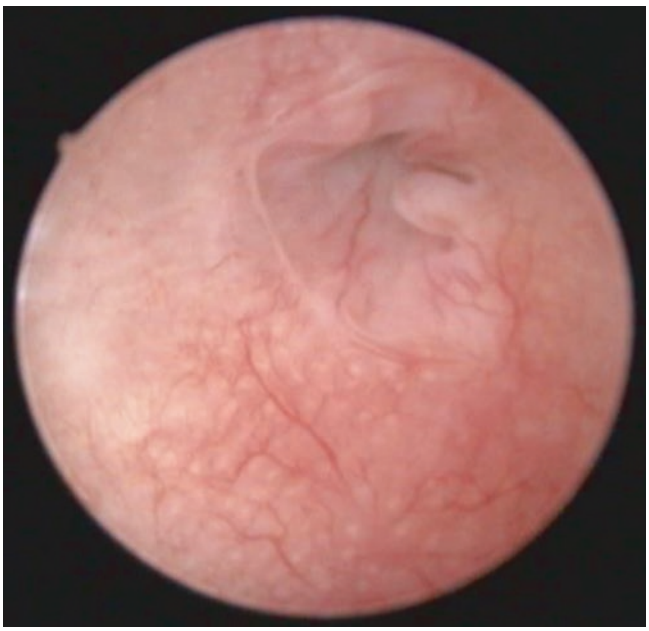


Fig. 22.4 Polyps

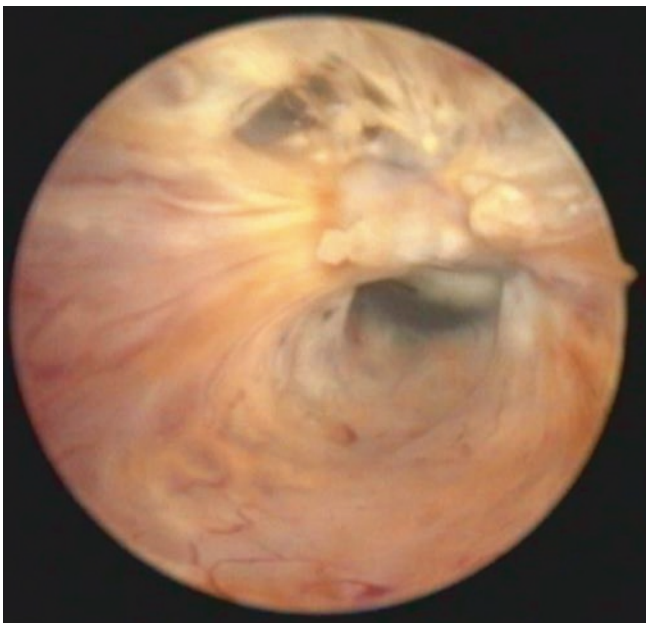
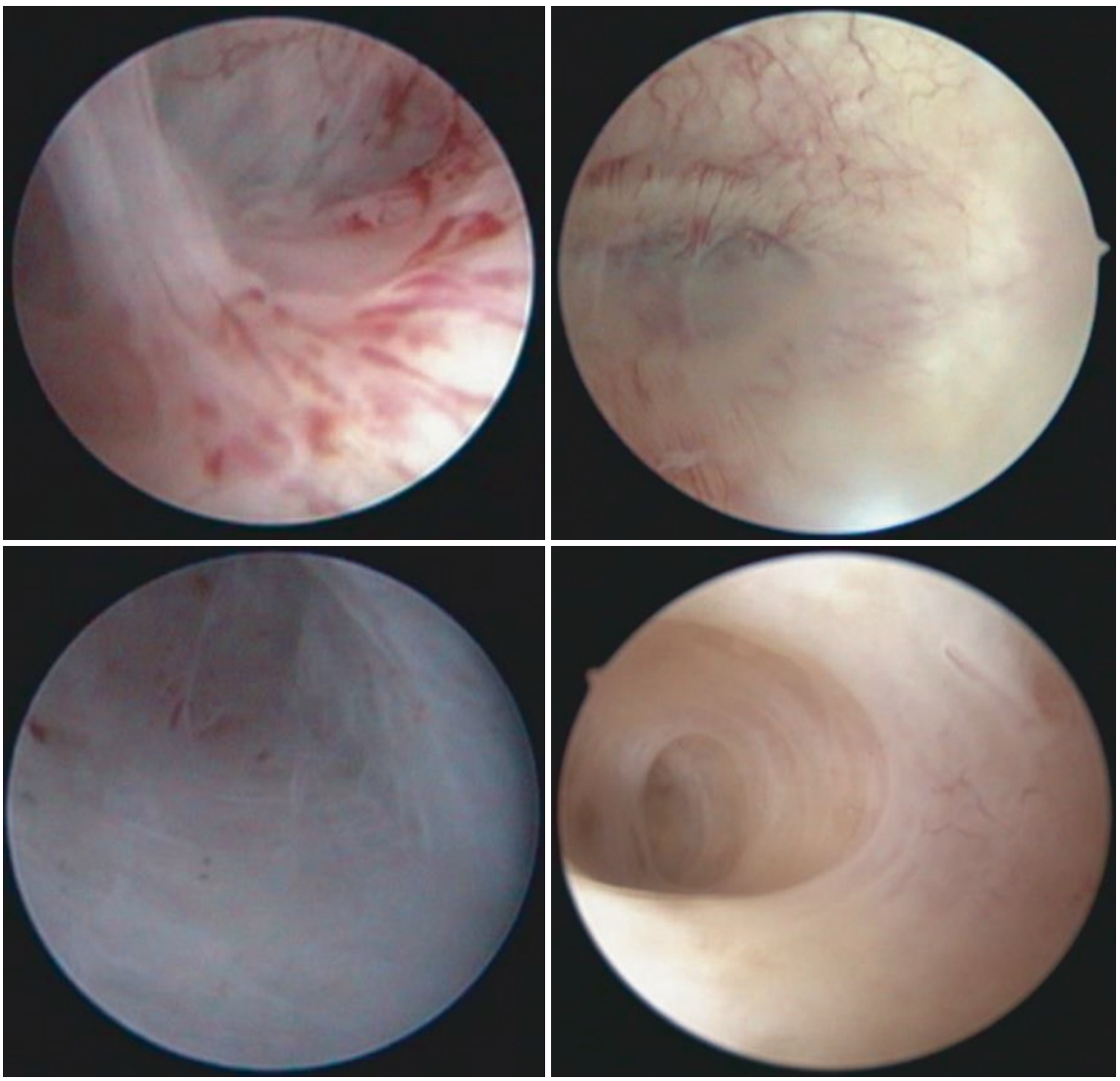


Fig. 22.9 Retained placenta at the fallopian tubal orifice



Figs. 22.5–22.8 Peritubal adhesions

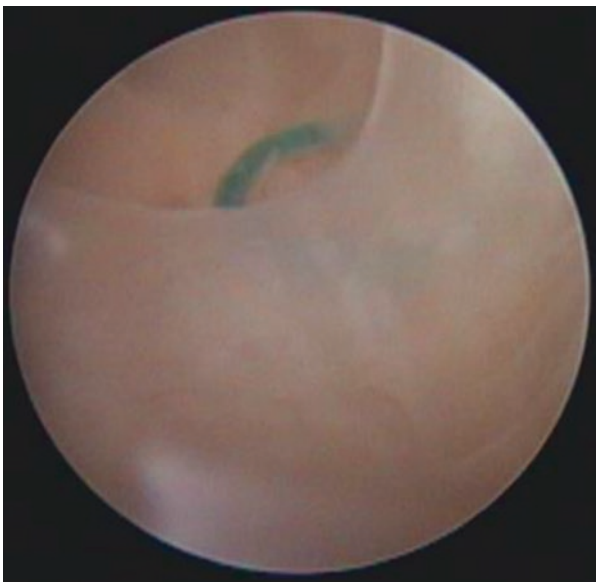


Fig. 22.10 Foreign bodies

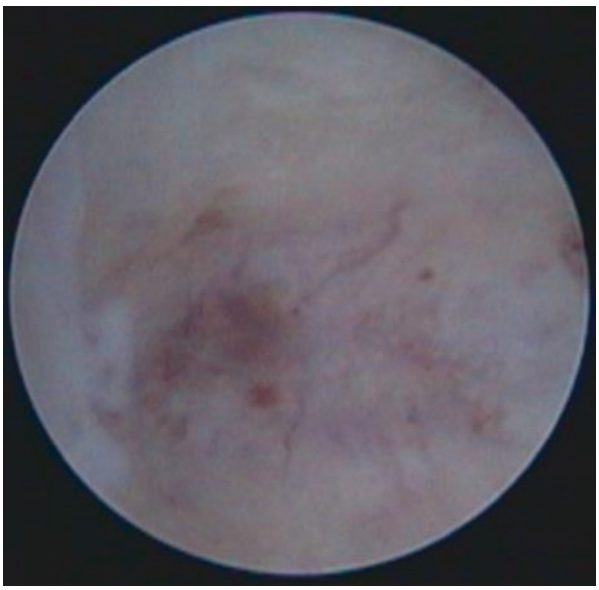
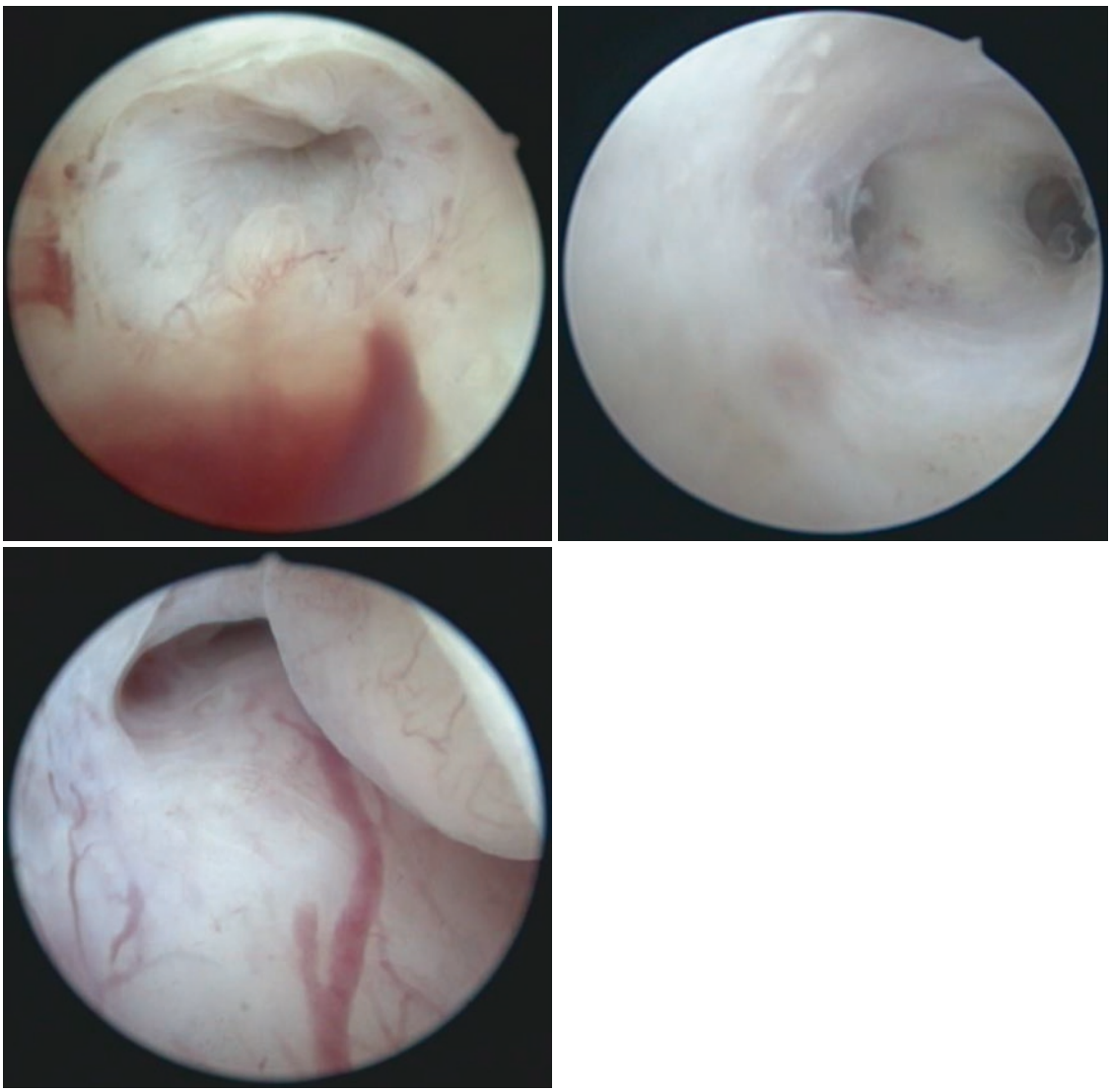


Fig. 22.14 Tubal orifice scarring



Figs. 22.11–22.13 Enlarged tubal orifice in hydrosalpinx

Fig. 22.15 Open tubal orifice

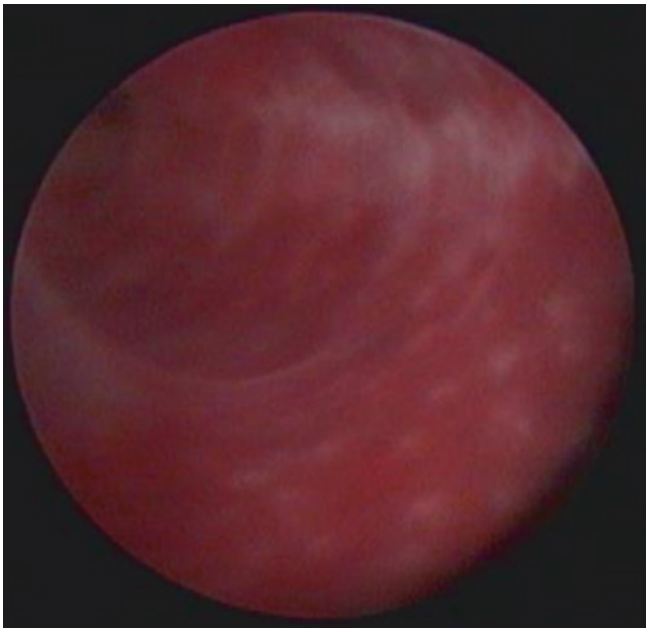


Fig. 22.17 Tubal imagine in case of uterine septum

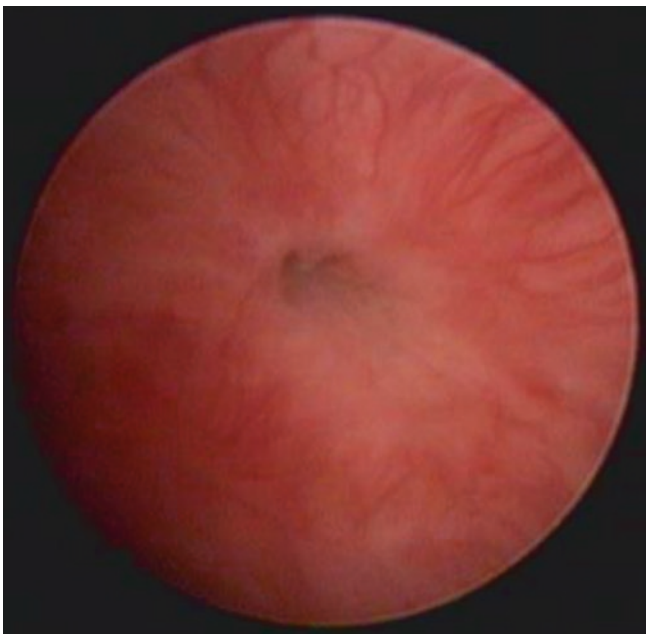


Fig. 22.16 Tubal occlusion supported by HSG

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Complications in Hysteroscopy

23

Bruno J. van Herendael

23.1 Introduction

Hysteroscopic surgery in general has a low risk of adverse events with an incidence of around 0.28% of 13,600 procedures according to a large Dutch multicentre study [1]. A similar incidence of 0.24% was found in a German observational study that included 21,676 procedures [2]. It is clear that the risk of complications is increased in more complex operative procedures; e.g. in hysteroscopic myomectomy the risk might be as high as 10% [3]. Complications of hysteroscopic surgery may be due to patient positioning, anaesthesia, access problems, use of distending media, gas emboli, perforation of the uterine wall, bleeding, use of instruments, or infection, or may be caused by the formation of intrauterine adhesions (IUAs), dissemination of endometrial cancer cells, or unwanted pregnancy [4]. Randomized controlled trials (RCTs) on the effectiveness of strategies to prevent complications do exist. A large body of the presented evidence on complications due to hysteroscopic surgery is based on observational studies.

23.2 Complications of Distension Media

23.2.1 Gas Distension Medium

Carbon dioxide is a very safe distension medium due to its rapid absorption into the blood and its clearance during pulmonary ventilation [5]. It is however not suitable for use during operative hysteroscopy or when the patient is bleeding. High-quality evidence from RCTs has demonstrated that the use of carbon dioxide is associated with increased patient discomfort, reduced patient satisfaction, and longer intervention times compared to the use of distension fluids [6, 7]. Significant adverse events have been reported in the literature, including gas emboli [8–10]. Therefore, carbon dioxide is almost never used in present-day hysteroscopic surgery.

23.2.2 Fluid Distension Media

23.2.2.1 Electrolytic Fluids

The isotonic electrolytic fluids most often used in operative hysteroscopy are normal saline and Ringer's lactate. In case of excessive intravascular absorption, their physiologic osmolality in general prevents hyponatraemia or hypo-osmolality. As a general principle, the excessive intravasation of isotonic electrolytic fluids will still lead to hypervolaemia, which is more amenable to treatment and less dangerous than fluid overload due to non-electrolytic fluids [11].

23.2.2.2 Non-electrolytic Fluids

Electrolyte-free low-viscosity media include 3% sorbitol, 1.5% glycine, 5% mannitol, and combined solutions of sorbitol and mannitol. In general, the excessive intravasation of this type of distending media will cause hypervolaemia in combination with hyponatraemia and hypo-osmolality. This may lead to the transurethral resection of the prostate (TURP) syndrome described in urological surgery. This potentially life-threatening syndrome is characterized by hyponatraemia, hypo-osmolality, nausea, vomiting, and neurologic symptoms including muscular cramping, blurring of the vision, grand mal seizures, agitation, if left inadequately treated, lethargy, coma, convulsions, and even death [12]. Premenopausal women are 25 times more likely than men or postmenopausal women to die or have permanent brain damage should hyponatraemic encephalopathy occur [13]. Moreover, pharmacologic complications may develop on top, related to some specific characteristics of the non-electrolytic distension medium used. Sorbitol is a reduced

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-29466-3_23) contains supplementary material, which is available to authorized users.

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A. Tinelli et al. (eds.), *Atlas of Hysteroscopy*, https://doi.org/10.1007/978-3-030-29466-3_23

form of dextrose; when absorbed in the systemic circulation, it is either excreted by the kidney or metabolized by the fructose pathway. Its use is therefore not suited for use in diabetic patients. Glycine is a non-conductive amino acid with a plasma half-life of 85 min; it is uniquely metabolized in the liver to ammonia and free water, further decreasing plasma osmolality. Due to its toxic effect on the central nervous system, its absorption is aggravated by a hyper-ammonaemic encephalopathy characterized by transient blindness, muscle pain, and memory loss. Mannitol is an isomer of sorbitol; it may act as an osmotic diuretic by increasing both the sodium and extracellular water excretion since it is not absorbed by the renal tubules [11].

23.3 Other Complications

Complications related to the patient positioning and anaesthesia: Nerve trauma, direct trauma, and acute compartment syndrome may be encountered as complications related to patient positioning in the lithotomy position [14]. Femoral neuropathy is due to a combination of excessive hip extension, abduction, and external hip rotation leading to an extreme angulation of the femoral nerve beneath the inguinal ligament and resulting in compression and damage to the femoral nerve. The sciatic and peroneal nerves are attached to the sciatic notch and the neck of the fibula, making them vulnerable to stretch injury. Excessive hip flexion, especially with a straight knee or excessive pressure over the head of the fibula from a stirrup, may lead to neural injury with a drop foot and lateral lower extremity paraesthesia. The acute compartment syndrome occurs when increased pressure in the muscle of an osteo-fascial compartment compromises local vascular perfusion causing ischaemia, leading to neuromuscular damage. This causes rhabdomyolysis and possible serious sequelae including permanent disability [15].

Finally, as is the case with any surgical procedure, there is a spectrum of anaesthesia-related complications that may be fatal for the patient. These include adverse events related to the use of anxiolytics and systemic analgesics in general anaesthesia and allergic reactions, systemic injection of local anaesthetics, and overdose associated with the use of local anaesthesia [16].

23.3.1 Trauma to Uterus and Cervix

Traumatic injuries caused by hysteroscopy are more frequent during operative hysteroscopy because more dilatation is necessary for the introduction of the larger calibre hysteroscopes [14]. Cervical lacerations are caused by the tenaculum during dilatation, especially when only one single-toothed instrument is used (Figs. 23.1, 23.2 and 23.3). If the bleeding is abundant, suturing may be required. The cervix or the uterus may be perforated during dilatation or insertion of the hysteroscope. The incidence of perforation varies from 4 to 13 per 1000 procedures [17]. Perforations caused by Hegar dilators require no treatment. Most full-thickness perforations are near the fundus if proper traction on the tenacula is applied (Figs. 23.4 and 23.5). In most cases, the procedure cannot be continued due to loss of adequate distension. Perforations due to the hysteroscopic procedure usually occur as a consequence of either poor visualization or lack of adequate uterine distension. When mechanical or thermal energy is used, visceral lesions may occur [18]. Anterior wall perforations may lead to bladder injury. Ureteral damage is associated with posterior or lateral perforations due to difficult operative manoeuvres. Perforations in the lateral uterine wall may cause vascular

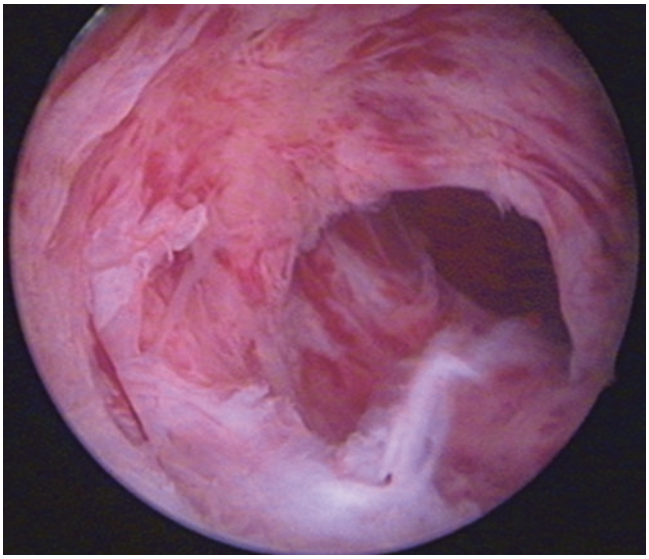

Fig. 23.1 False Passage at the cervical level Courtesy G. Vilos

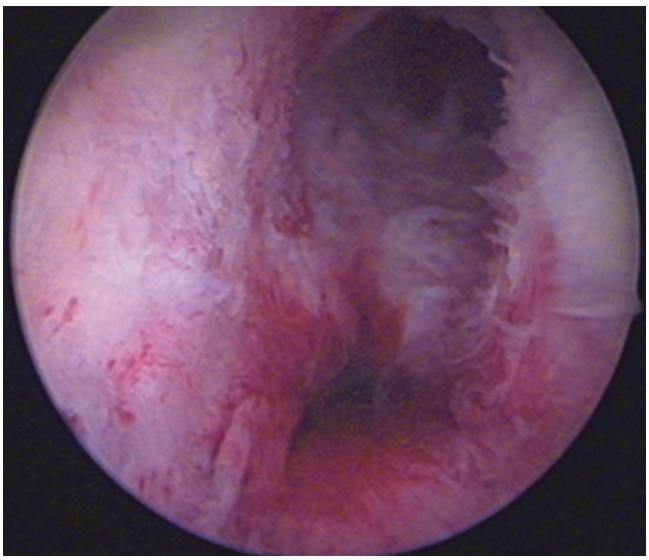

Fig. 23.2 False passage at the cervical level with dillators. Normal cervical canal lower part, false passage upper part. Courtesy G.Vilos

Fig. 23.3 Dilator perforating at the levelo of the cervix visible to the right of the image Courtesy G. Vilos

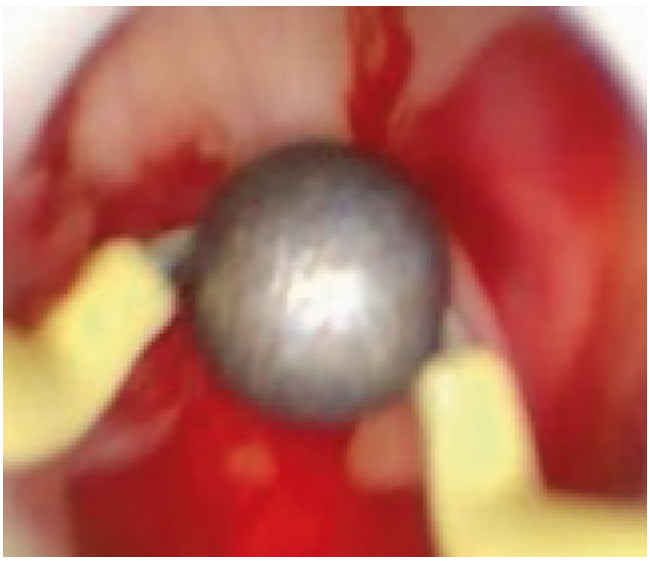

Fig. 23.4 Perforation posterior wall full tickness low in uterine cavity by dilators bowel fat visible under the rollerball

lesions in the iliac vessels, mesenteric artery, aorta, and presacral vessels [19]. These lesions may cause broad ligament hematomas or significant haemorrhage and should be treated without any delay when diagnosed or suspected. Any perforation associated with the concomitant use of electrosurgery or laser carries a high risk of visceral injury. These cases should be explored by laparoscopy for damage to the bladder, ureters, bowel, and vessels (Fig. 23.6a, b). In doubt, a laparotomy should be done to discount visceral trauma fully. Patients treated or suspected for visceral injury should be kept under close medical surveillance for several days until full recovery. Penetrating thermal injury to the bowel can be managed successfully with primary repair [20].

Fig. 23.5 Perforation at the uterine fundus by the resectoscope courtesy G.Vilos

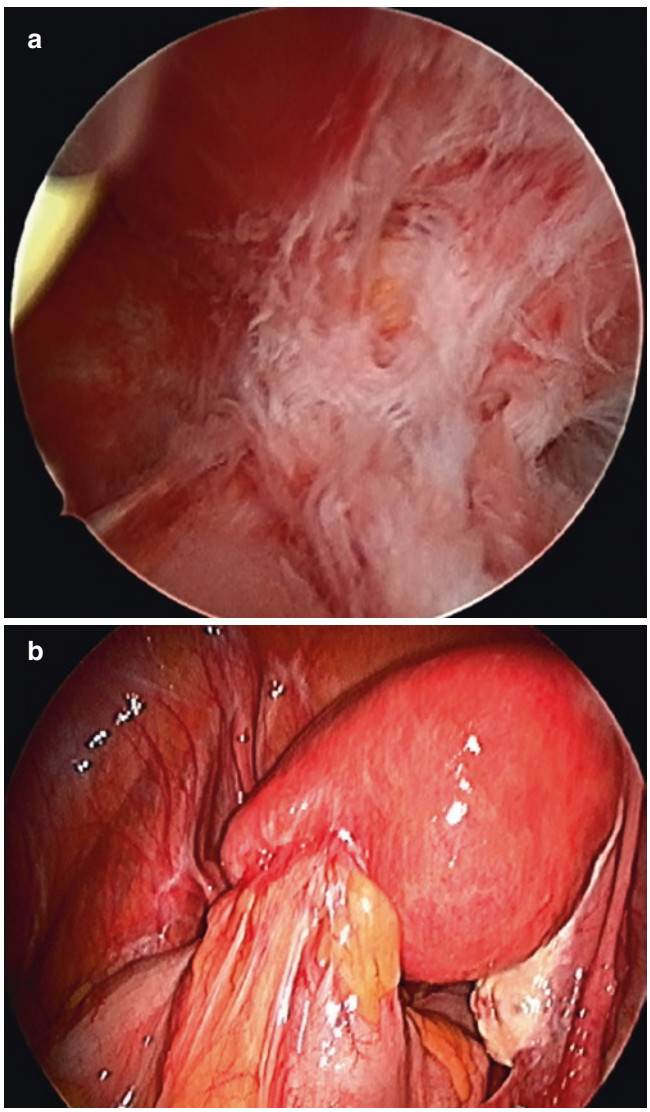

Fig. 23.6 (**a**) Uterine cavity delayed perforation due to interference of monopolar current. (**b**) Laparoscopic view: incarceration of the bowel in the uterine wall due to delayed perforation. Courtesy G. Vilos

23.3.2 Air or Gas Embolism

Air embolism is a very rare but potentially fatal complication of hysteroscopic surgery. It was documented in relation with hysteroscopic surgery for the first time in 1985. An overview of several cases including fatalities has been published in the literature [21]. An overview included 13 cases with a mortality rate of nearly 50% [10]. The early detection of gas or air embolism based on altered electrocardiographic patterns, an acute rise in the pulmonary artery pressure, or aspiration of air from a central venous line should lead to stop the procedure, turning the patient to the left side to elevate and keep gas in the right side of the heart and start cardiopulmonary resuscitation. During any hysteroscopic procedure, slight anti-Trendelenburg position can be adopted to minimize the negative aspiration pressure during the cardiac cycle. Cervical trauma should be minimal and the cervical canal should be occluded as long as possible—leaving the Hegar dilator in situ after dilatation to be replaced by the operative hysteroscope. It is likewise important to try to minimize taking in and out the instruments as much as possible (Trombone playing).

23.3.3 Bleeding

Intra- or postoperative bleeding is the ***second most common*** complication of hysteroscopic surgery: it occurs in 2.5 per 1000 procedures [22]. The incidence rates are higher for hysteroscopic resection of fibroids, especially with an intramural component (2–3%), and for endometrial ablation or resection procedures (0.2–2.2%) [23]. Problematic bleeding during an operative hysteroscopy is rare because the pressure of the distension medium decreases blood loss from venous vessels. Electrocoagulation with a wire loop or a rollerball or barrel can stop such bleeding. At the end of the procedure, decreasing the intrauterine pressure while visualizing the entire uterine cavity can reveal any occult bleeding. To stop troublesome bleeding at the end of the procedure, a Foley catheter may be inserted in the uterine cavity and its balloon may be filled with 20–30 mL of saline. Take into account that this manoeuvre is extremely painful for the patient. The balloon catheter may be removed in 2–24 h [24]. In case of intractable bleeding, vasopressin (20 U in 20 mL normal saline) may be injected into the cervix to inhibit bleeding from the lower segment. Misoprostol can be given intrarectally if needed. If these methods fail, uterine artery embolization may be considered by an interventional radiologist. If all other methods fail, hysterectomy may be indicated in case of profuse life-threatening bleeding [18].

23.3.4 Infection

The incidence of endomyometritis following hysteroscopy is extremely low, ranging from 0.01 to 1.42% [14]. Routine antibiotic prophylaxis is not recommended for the general population undergoing hysteroscopic surgery according to the ACOG (2009) (level B recommendation according to the method described by the US Preventive Services Task Force) and Society of Obstetricians and Gynecologists of Canada (SOCG) guidelines (II-2D using the Canadian Task Force on Preventive Health Care System for the quality of evidence assessment) [25, 26]. The risk of infection may be higher in patients with a history of PID ; therefore, the ACOG guideline states that antibiotic prophylaxis may be considered for hysteroscopic interventions in women with a history of PID or tubal damage (2009) (level C recommendation) [25].

23.3.5 Late Complications

IUA formation is the major long-term complication of operative hysteroscopy in women of reproductive age. According to an RCT on the effectiveness of preoperative treatment before operative hysteroscopy, the incidence of postsurgical IUAs at second-look hysteroscopy was 3.6% after polyp removal, 6.7% after resection of uterine septa, 31.3% after removal of a single fibroid, and 45.5% after resection of multiple fibroids [27]. The postoperative formation of IUAs is undesirable in women wishing to conceive or to preserve their fertility. The removal of fibroids on opposing walls probably increases this risk. Recurrence of intrauterine synechiae is even more challenging. When extensive adhesions are lysed, little normal endometrium may remain to be re-epithelialized and the risk of recurrence is very high. Especially in the lateral and fundal parts, it is very difficult to keep the walls separated [18].

23.3.6 Haematometra

Haematometra following an endometrial resection or ablation occurs very infrequently: about 1–2% of women will develop symptomatic haematometra following these procedures [28]. Cyclic or chronic lower pelvic pain is the most dominant symptom. Most cases can be treated by cervical dilatation, although some cases need to be treated by synechiolysis to approach haematometra in the uterine fundus [28]. Identifying and avoiding the lower uterine segment and cervix are very important in the prevention of haematometra. For decreasing the risk of a post-ablation tubal sterilization syndrome, the endometrium in the cornual region should be effectively destroyed (Fig. 23.7) [29].

23.3.7 Unplanned Pregnancy

Pregnancies do occur after hysteroscopic sterilizations [29]; however, they are less common with the newer generation devices. Unplanned pregnancies may be observed in women who were not sterilized previously following endometrial

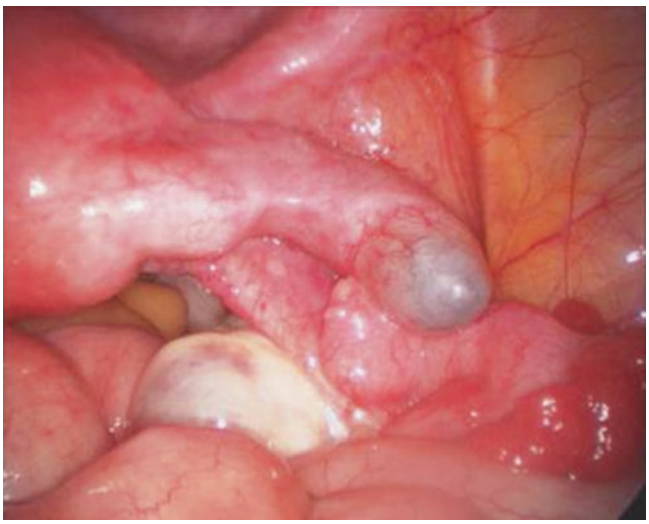

Fig. 23.7 Post Ablation Sterilization Syndrome (PATSS). Courtesy G. Vilos

ablation. The incidence in the literature varies from 0.2 to 1.6% [30]. Pregnancies following operative hysteroscopic procedures must be considered as being at high risk of a variety of medical problems, including miscarriage, ectopic pregnancy, uterine rupture, premature birth, intrauterine growth restriction, and higher risk of placenta accreta/percreta [4]

23.4 Dissemination of Endometrial Cancer Cells

A recent systematic review and meta-analysis [31] have demonstrated a significantly higher occurrence of malignant peritoneal cytology following hysteroscopy versus no hysteroscopy in women with proven endometrial carcinoma [the odds ratio (OR) was 1.8, 95% confidence interval (CI) 1.1–2.8, $P = 0.013$, 9 studies, 1015 women]. There was a higher rate of disease upstaging compared with no hysteroscopy (OR 2.6, 95% CI 1.5–4.6, $P = 0.001$, 9 studies, 1015 women). The use of normal saline increased the rate of malignant peritoneal cytology compared to no hysteroscopy (OR 2.9, 95% CI 1.5–5.6, $P = 0.002$, 9 studies, 1015 women); there was no evidence for an increased occurrence of malignant endometrial cells in the peritoneal cytology in the intervention group when inflated media pressure reached or exceeded 100 mmHg (OR 3.2, 95% CI 0.94–11, $P = 0.06$).

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